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# AGAMMAGLOBULINEMIA.

## Report of Two Cases and Review of Literature.*

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The early symptoms and signs of many diseases are referable to the upper respiratory tract. A recently discovered abnormality of the plasma proteins, agammaglobulinemia† or hypogammaglobulinemia, is no exception.

In this syndrome there is a low or absent Gamma globulin, and as a result individuals suffering from this disorder are unusually susceptible to repeated and severe bacterial infections. Infections of the nose, sinuses, ears, throat, lungs, and meninges are quite common in the majority of these patients, and for this reason the otolaryngologist should be thoroughly familiar with agammaglobulinemia; therefore, the purpose of this paper is to review comprehensively the literature on this subject and to present two cases illustrating the characteristic features of this disease.

### DEFINITION.

Agammaglobulinemia is a congenital or acquired syndrome, the cardinal features being *1.* increased susceptibility to bacterial disease, with a history sometimes dating to childhood; *2.* marked deficiency of circulating plasma Gamma globulin; *3.* absence of circulating antibody in the blood tissues; and

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†The term agammaglobulinemia, which has been established by precedent, will be used in this paper although there is seldom a complete absence of Gamma globulin in the serum of patients with this condition.

4. failure of antibody production in response to antigenic stimulation.[1,2]

The normal range of serum Gamma globulin is about 600 to 1200 mg. per 100 cc. of serum.[1] Although the term agammaglobulinemia implies an absence of Gamma globulin in the plasma, the deficiency is usually not complete. The level of Gamma globulin is usually less than 30 mg. per 100 cc. of serum.[1] Clinical experience has indicated that a circulating concentration of Gamma globulin of more than 100 to 150 mg. per 100 cc. is necessary to provide protection against bacterial infections;[1] therefore, to make the diagnosis of agammaglobulinemia the serum Gamma globulin should not be greater than 150 mg. per 100 cc. of serum (about 2 per cent of the total protein per 100 cc. of serum).

## CLASSIFICATION.

Individuals having very low levels of circulating Gamma globulin may be divided into four groups: *1.* congenital agammaglobulinemia; *2.* acquired or adult agammaglobulinemia; *3.* secondary hypogammaglobulinemia; and *4.* transient or physiologic hypogammaglobulinemia. Patients in the first three groups have a permanent defect of their antibody-producing tissue. Newborn infants comprise the fourth group and have only a temporary lowering of the Gamma globulin level.

*Congenital Agammaglobulinemia.* This is a syndrome observed in children and is characterized by recurrent bacterial infections beginning in infancy or very early childhood where there is an inability to synthesize Gamma globulin from birth.[1,3,4] The incidence strongly suggests that this defect is inherited as a sex-linked recessive characteristic like that of hemophilia.[1,4] Thus, it is transmitted by women, who are otherwise normal, to one-half of their male offspring. A few cases of congenital agammaglobulinemia have been reported in females.[5,6] Gitlin and Janeway[1] have not substantiated a diagnosis of congenital agammaglobulinemia in any of the female children which they have studied; however, they point out that this type of inheritance pattern statistically *does* permit the rare possibility of this disease occurring in a

female child. In these cases there is often a suggestive familial history. There may be a history of one or more male relatives having died from an overwhelming infection early in childhood. Symptoms usually appear at about six months when the infant has used up the Gamma globulin which he received from his mother. Many of the children handle themselves well until the age of three or four years. Before the days of antibiotics, many of these children apparently succumbed to their first or second major infection.

*Acquired or Adult Agammaglobulinemia.* This syndrome is so named because of its apparent onset later in life, although it has been observed in older children. It differs in several respects from the congenital form. It may occur in males or females. There is lack of a familial tendency. It is manifested by recurring bacterial infections, which begin at any time from childhood to old age, and which are associated with a severe hypogammaglobulinemia.[1] These patients apparently handle infection well until suddenly they lose the ability to form antibodies. Consequently, they suffer many bacterial infections.

*Secondary Hypogammaglobulinemia.* Low or measurably absent serum Gamma globulin is frequently observed as a manifestation of many systemic diseases.[2] Apparently, these patients develop hypogammaglobulinemia as a result of some diffuse disease of the reticuloendothelial system which interferes with the production of antibodies by normal plasma cells.[4] This finding is noted frequently in pediatrics in association with nephrosis.[2] Leukemia, lymphoma and myeloma may cause hypogammaglobulinemia.[4,7] Porges[8] has described a method for demonstrating secondary agammaglobulinemia in the presence of abnormal myeloma protein. His results suggest that an absence of normal Gamma globulin can occur in multiple myeloma even when electrophoresis and other tests indicate abnormal amounts of Gamma globulin. He reported absence of normal Gamma globulin in two patients with myeloma. The first patient had episodes of pneumonia, otitis media and sinusitis. The second patient had recurrent attacks of pneumonia. This finding would account for the increased susceptibility to infection which is seen in some

patients with multiple myeloma. Other causes of secondary hypogammaglobulinemia include total body irradiation and treatment with mechlorethamine hydrochlorid (nitrogen mustard).

*Transient or Physiologic Hypogammaglobulinemia.* This constitutes a state of temporary deficiency in circulating plasma Gamma globulin resulting from an accentuation of the normal inadequacy of Gamma globulin synthesis in the first few months after birth.[1] Serum Gamma globulin levels are normal in the newborn infant, but drop by about one-third in the first month of life.[10] They remain at these levels for about three months and then gradually begin to rise. Normal adult values are reached at the age of two years.

The newborn infant acquires the major portion of his Gamma globulin from the maternal circulation. The fact that he does not synthesize Gamma globulin in adequate amounts until one to three months after birth accounts for the physiologic and transient fall in Gamma globulin the early months of life. The normal infant is born with 1,000 mg. per 100 cc. of serum Gamma globulin, and most infants produce Gamma globulin to keep their total serum concentration from falling below 300 mg. per 100 cc.[9] Gitlin and Janeway[1] have observed two infants with serum levels of 75 to 150 mg. per cent of Gamma globulin who had severe infections. Thus, this period of transient hypogammaglobulinemia in an infant's life may be a hazardous one, particularly in the premature infant. Because of this physiological lowering of the Gamma globulin in infants, one must be extremely cautious in establishing a diagnosis of congenital agammaglobulinemia in an infant below six or eight months of age, especially if the infant is a female.

## ETIOLOGY.

The symptoms of agammaglobulinemia are directly related to the deficiency or absence of circulating Gamma globulin.[1] In congenital agammaglobulinemia Gamma globulin is also absent in the tissues; thus, the circulating deficit is part of a total body deficit.[1] The biologic defect in this disease is a failure of synthesis of Gamma globulin.[1] The fact that ad-

ministered Gamma globulin circulates in patients with agammaglobulinemia for as long as it does in normal persons indicates that the basic defect is failure to synthesize Gamma globulin rather than abnormally rapid destruction or loss.[9]

A profound disturbance of the hematopoietic system accompanies agammaglobulinemia. Recent evidence points toward plasma cells or lymphocytes as the principal sites of antibody and Gamma globulin formation.[3,11,12] Recent studies based on the assumption that antibodies are produced by immature plasma cells and lymphoblasts have shown that the lymph nodes of patients with idiopathic low and absent Gamma globulin do not respond with plasmocytosis to antigenic stimulation.[13,14,15] In a few cases changes have been observed in bone marrow, namely, the marked reduction of plasma cells.[16] That this finding may be a clue to the etiology is the fact that occasionally there is noted an absence of Gamma globulin in multiple myeloma,[17] a disease characterized by derangement of plasma cells. Possibly more than one cell is concerned, as opinions vary as to the development and morphology of cells. To support this theory, Good and Campbell,[18] using quantitative bone marrow counts of plasma cells, have been able to correlate plasmacytosis with elevation of serum Gamma globulin in patients with rheumatic fever.

The plasma cell (Plasmacyte) was discovered by Cajal in 1890.[19] A preponderance of evidence favors the reticuloendothelial cell as the probable forerunner of the plasma cell.[12,20-24] In regard to function, Bing and Plum[25] in 1937, were the first workers to call attention to the relationship of plasmocytosis and hyperglobulinemia. Now it is fairly well established that antibodies are produced, for the most part, by the precursor of the plasma cell.[25] Paris, et al.,[23] reported a patient with agranulocytosis of the aplastic type, with an unusually extensive reactive plasmocytosis of bone marrow, *i.e.*, 60.2 per cent, and a hyperglobulinemia of 3.08 gm. per 100 ml. In this patient there was hyperplasia of the reticulum cells within bone marrow, lymph nodes, and spleen; in addition, in the bone marrow, transitional forms were observed which were morphologically intermediate between reticulum cells and plasma cells. These findings support the concept

of the reticuloendothelial origin of the plasma cell. Good's findings support the concept that plasma cells are directly involved in the sequence of events resulting in the formation of antibodies and Gamma globulin.[26] Evidence in the literature demonstrates conclusively that plasma cells form antibodies in experimental animals.[26]

Most of the pathological changes reported in agammaglobulinemia have been those secondary to repeated or long-standing infections.[27] Janeway, et al.,[28] reported that an autopsy on a patient with agammaglobulinemia revealed only a strikingly diminished Gamma globulin content of the lymphoid tissue, and that a connective tissue biopsy on a patient with this disorder showed a low Gamma globulin content. Function tests, biopsies, and postmortem studies show that hepatic dysfunction is not responsible for failure of Gamma globulin synthesis.[29] The clotting mechanism is normal in patients with this disorder.[29] Lymph nodes of patients with agammaglobulinemia tend to be small, poorly developed, and have a relatively thin cortex with few germinal centers.[26] As has been mentioned previously, lymph nodes and bone marrow of these patients are characterized by failure to develop plasma cells and secondary follicles in response to both primary and secondary antigenic stimulation.[26]

The patients originally described by Bruton and associates were boys, and it was assumed for a time that the disease occurred only in males and was genetically determined, being transmitted as a sex-linked recessive trait. While it is true that most of the patients are boys who have a congenital absence of Gamma globulin, this syndrome has been reported in two females.[5,6] An acquired form of this disease is now recognized which affects both males and females of all ages.[4,17,30-36] Two possible mechanisms in the pathogenesis of agammaglobulinemia have been suggested, one being a sex-linked hereditary process as seen in young males, and the other in adults of both sexes being acquired from some sort of assault on the Gamma globulin producing function.[17] Seltzer, et al.,[15] reported a case of agammaglobulinemia in an adult male who had had histoplasmosis. They raised the question as to whether histoplasmosis and the resulting infection of the antibody-

forming reticuloendothelial system may have resulted in depression of Gamma globulin; however, there is reason to believe that both congenital and acquired agammaglobulinemia are hereditary, for as Brem and Morton[27] point out, it is difficult to envision a noxious agent which can pick out one specific function and eliminate it entirely without damaging related functions. They state that the elimination of a single protein fraction is much more characteristic of a hereditary process in which the gene for that particular function is defective, afibrinogenemia and hemophilia being notable examples of this process. In support of the hypothesis that the acquired type may also be congenital is the fact that many inherited diseases make their appearances at widely varying ages. There is a distinct possibility of an inherited basic biologic defect manifesting itself in delayed failure of Gamma globulin production.[37] That failure in Gamma globulin synthesis is responsible for the deficiency in adult agammaglobulinemia has been indicated by the demonstration of a normal rate of degradation of administered radioiodinated Gamma globulin.[37,38]

Brem and Morton[27] remind us that the Gamma globulin fraction is composed of a heterogenous group of globulins with different physical and chemical properties, and that one of the perplexing aspects is that the whole Gamma globulin fraction can be virtually eliminated at once. They deduce that since there is a simultaneous elimination of the whole fraction, all of the Gamma globulin is elaborated by a highly specialized tissue, and that the function of this tissue can be deranged in varying degrees.

Of particular interest is the fact that cases of acquired agammaglobulinemia have been reported in patients with multiple congenital deformities;[34,37,39] moreover, this disorder has been described in siblings.[27] Various authors have reported hypergammaglobulinemia in parents of patients having acquired agammaglobulinemia;[37,40,41] thus, the association of this syndrome with congenital deformities, its occurrence in siblings, and the existence of hypergammaglobulinemia in parents of some cases, strongly suggest a hereditary basis in the etiology of acquired agammaglobulinemia.

Varco, et al.,[42] describe the homotransplantation of skin in two children suffering from congenital agammaglobulinemia. This is in sharp contrast to the observation that normal persons always reject grafts from unrelated donors. In these patients immunological studies indicated a complete immunologic paralysis. In an adult with acquired agammaglobulinemia they reported the delayed rejection of a skin homotransplant. They describe this patient as having an incomplete immunological paralysis. These experiments demonstrate dramatically the inability of patients with this condition to produce antibodies, and support the theory that rejection of homografts has an immunologic basis.

## CLINICAL MANIFESTATIONS.

The symptoms of agammaglobulinemia are primarily those of infection. Since the manifestations of infection are quite varied, each patient presents an individual problem. These patients are unusually susceptible to bacterial infections, and many of them have repeated severe crippling diseases. Sinusitis, otitis media, pneumonia, meningitis and bacteremia follow each other with extreme rapidity. The individual pattern of infection and the severity of any one episode are highly variable. Gitlin and Janeway[1] point out, that while meningitis has occurred in a single child on two or even three separate occasions, in the same child attacks of pansinusitis and otitis media were far more frequent.

Some patients develop chronic bacterial infections, such as chronic otitis media, chronic pansinusitis, and bronchiectasis. There is no specific characteristic of any of the infections that would implicate the diagnosis of agammaglobulinemia; thus, the presenting symptoms of patients suffering from this disorder are quite protean, some having bronchiectasis and pneumonia and others arthritis, pyoderma with septicemia, and even severe gastro-intestinal conditions. Gitlin and Janeway[1] surveyed a great many children who were subject only to repeated attacks of tonsillitis and upper respiratory infections, and did not find any with congenital agammaglobulinemia.

The role of antibiotics in the defense against bacterial

infections is well demonstrated in patients with agammaglobulinemia. Although these patients have an unbelievable number and variety of illnesses, the infections may be no more severe than those observed in normal individuals. The bacterial infections in these individuals respond to treatment with chemotherapeutic and antibiotic agents.[4] This fact may explain why this condition was not recognized clinically until after the antibiotic era, for prior to that time there is a good possibility that patients with absent Gamma globulin did not survive long enough to establish a history of recurrent infections.

One of the unusual features of this condition is the apparent ability to deal with virus infections.[43] The observation has been made that patients with this anomally have had measles, mumps, chickenpox and poliomyelitis with no greater frequency or severity than normal individuals.[4] This is true of both children and adults.[43] Thus one would conclude that immunity to virus infections is not wholly dependent on Gamma globulin, or that smaller amounts of the substance are needed to protect against viruses than against bacteria. One case has been reported to have had three attacks of parotitis, but the diagnosis of mumps as against recurrent parotitis could not be confirmed.[44] One exception to the general rule is apparent susceptibility to vaccinia virus. Carson and Connell[45] reported a fatal case of vaccinia gangrenosa in a nine-month-old white infant with hypogammaglobulinemia. Four similar cases have been reported in the literature.[5,46-48] A few children with low Gamma globulin, without pre-existing skin involvement, have apparent inability to produce vaccinia virus neutralizing antibodies either in sufficient quantity or quality.[45] In such children generalized vaccinia with severe necrotizing lesions may develop; on the other hand, many patients with agammaglobulinemia have been vaccinated without complications.[28,44,45]

Patients with agammaglobulinemia have a severe immunologic handicap.[4] Immunologic reactivity is paralyzed or extremely slight. Dick and Schick tests are uniformly positive. As antibody responses cannot be provoked by antigenic stimulation, immunization against disease by usual means is im-

possible.[29] Gitlin and Janeway[1] have been unable to demonstrate reagins in many of these children tested with the pollens of numerous grasses and trees, and with antigens prepared from allergenic foods.

Moderate to severe degrees of neutropenia have been reported in children with agammaglobulinemia.[1] This is believed to represent a secondary factor in this disease resulting most likely from toxic effects of the infections. It is cyclic, and recovery from leukopenia does not always parallel recovery of the patient from an infection. In most cases, however, there is a prompt rise in granulocytes with infections even in those children showing neutropenia.[1]

Recently attention has been drawn to the association of agammaglobulinemia with enlargement of the liver, spleen and lymph nodes. Citron[40] described two cases and reviewed six similar ones in the literature with hepatosplenomegaly and lymph node enlargement. The chief histological features were diffuse reticuloendothelial hyperplasia and deficiency of plasma cells. Pearce and Perinpanoyagam[6] reported hepatosplenomegaly and palpable cervical lymph nodes in a case of congenital agammaglobulinemia. Three cases of acquired agammaglobulinemia with hepatosplenomegaly have been described by Martin, et al.[49] Savacool and Landes[50] reported splenomegaly and lymph node enlargement in a 38-year-old male with acquired agammaglobulinemia. Zelman and Lewin[37] described reticuloendothelial hyperplasia of spleen and lymph nodes with granuloma formation in a patient with acquired Gamma globulin deficiency.

Of particular significance are the instances of arthritis and dermatomyositis which occur in patients with congenital and acquired agammaglobulinemia.[51,52] Cases of suppurative arthritis have been observed, but these probably are of the same general nature as the other infections which plague these patients. Of special interest is the nonsuppurative form of arthritis which has occurred in roughly a fourth of recorded cases.[51] Individual joints present clinical features quite consistent with rheumatoid arthritis, including effusions, slight local warmth, pain and tenderness, and slight to moderate limitation of motion. Synovitis consistent with rheuma-

toid arthritis has been described in biopsy specimens of synovial membrane.[51]

The occurrence of dermatomyositis in patients with agammaglobulinemia lends support to the view that this is truly rheumatoid arthritis;[52,53] however, Vaughan and Good[54] tested patients with agammaglobulinemia by several procedures for demonstration of the rheumatoid factor or its inhibitor, and found neither agglutinator nor inhibitor in the sera of the patients studied. They could neither confirm nor exclude a possible relationship between the arthritis of agammaglobulinemia and rheumatoid arthritis. One suggestion as to the possible mechanism of causation is that the arthritis of agammaglobulinemia is an inflammatory response to non-living products of repeated chronic infections.[51] Fortunately, most attacks of arthritis accompanying agammaglobulinemia have subsided spontaneously over periods of several days to months without residual disability.

Acquired agammaglobulinemia differs from the congenital type in that the outstanding clinical features are pulmonary and gastrointestinal manifestations.[1] According to Mazzitello and Good,[43] pulmonary infection represents a *sine qua non* of the agammaglobulinemia syndrome. Bronchiectasis is a particularly threatening disease. Though it has been seen in patients with the congenital type it is more common in acquired agammaglobulinemia.[43] From this it follows that agammaglobulinemia should be ruled out in all cases of bronchiectasis.

## DIAGNOSIS.

A variety of laboratory studies have been suggested to assist in establishing the diagnosis of agammaglobulinemia. Barrett and Volwiler[9] have separated the tests into two groups: presumptive and definitive.

### *Presumptive Tests.*

Many routine laboratory tests suggest the diagnosis of agammaglobulinemia. The tests below aid in the diagnosis but do not definitely prove or exclude the presence of the condition.

*Total Serum Globulins:* Since about one-half of the reported concentration is Gamma globulin, agammaglobulinemia may cause a low level of total globulin. Of course, if the patient has a chronic disease causing an increase of the other globulin fractions, the level of total globulins may be within normal limits.

*Isohemagglutinin Titers:* Patients with agammaglobulinemia have shown a deficiency in isohemagglutinins, and demonstration of their absence during blood grouping has been suggested as a screening test for the disease in patients with blood groups O, A and B. The test is of no value for patients with blood group AB. A normal person who is not of type AB and who is over two years of age usually has a titer of anti-A or anti-B of 1:8 or higher. A high titer would rule out the disease, and a low titer would strongly suggest it.

*Response to Antigenic Stimulation:* Patients with agammaglobulinemia have persistently positive Schick and Dick reactions. This is true since lacking Gamma globulin they do not produce antibodies. Antibody formation may be determined by injecting antigens such as typhoid and diphtheria vaccines. A good antibody response, as measured by the Gruber Widal reaction and the Schick test, tends to rule out agammaglobulinemia.

*Zinc Sulfate Turbidity Test:* Good[29] recommends zinc turbidity as a simple screening test. It gives a semiquantitative estimate of the concentration of Gamma globulin in the serum. Values of zero to one unit are compatible with the diagnosis of agammaglobulinemia. Higher values rule it out.

*X-ray Findings:* Margulis, et al.,[55] report the important diagnostic Roentgen features of agammaglobulinemia as being extensive pulmonary parenchymal disease with paradoxical absence of hilar node enlargement and the striking deficiency of nasopharyngeal lymphoid tissue, in spite of recurrent upper respiratory infections. Many of the patients showed pansinusitis. Chest and sinus X-rays with a soft tissue lateral view of the nasopharynx should be routine on any patient suspected of having this disease.

*Definitive Tests.*

There are two definitive tests for agammaglobulinemia—electrophoresis of the serum and immunochemical quantitation.

*Electrophoresis of Serum:* This is a procedure for direct measurement of the Gamma globulin content of the serum plasma. Paper electrophoresis, as described by Durrum, is one of the most reliable screening tests for agammaglobulinemia. The technique is simple, and only a small quantity of blood is needed. The Gamma globulin is usually reported as a percentage of the total protein per 100 cc. of serum. Normal values range from 12 to 16 per cent. Free electrophoresis as described by Tiselius is also satisfactory, but more equipment and a larger sample of blood are required. By either of these techniques the only significant abnormality of the serum proteins in patients with agammaglobulinemia is an absence or marked decrease of the Gamma globulin.

*Immunochemical Quantitation:* Immunochemical methods offer the only satisfactory means of sensitively measuring low concentrations of Gamma globulin.[9] The precipitin method seems to be the best of these techniques. There is actually some Gamma globulin in the serum of these patients, but not enough to be demonstrated by electrophoresis.[4] Using the immunochemical techniques, analysis of the plasma of patients with congenital and acquired forms of the disease shows the presence of small amounts of Gamma globulin. Patients with acquired agammaglobulinemia have slightly more Gamma globulin than patients with the congenital type. In both types the concentration seldom exceeds 100 mg. per 100 cc. of serum (normal 600 to 1,200 mg. per 100 cc.).[4]

## TREATMENT.

In the therapy of agammaglobulinemia both antibiotics and concentrated Gamma globulin have proven of value.[1] The prime considerations in the treatment of a patient who is unable to produce antibodies are: *1.* the rapid control of acute infections, and *2.* the prevention of recurrent infections.[9] In the treatment of acute bacterial infections the same principles as are efficacious in treating such infections in immunologi-

cally normal persons are regularly successful.[43] There should be accurate bacteriologic diagnosis and intensive specific treatment. In addition, time-honored procedures of surgical drainage in acute and chronic infections should be employed when indicated. Pooled Gamma globulin apparently does not alter the course of an acute disease in these patients.[9] This would be expected, since it does not provide enough specific antibody to a single bacterial antigen. Thus, Gitlin and Janeway[1] state that in their patients, the use of antibiotics has proven more effective than the use of Gamma globulin alone in the treatment of acute infections.

On the other hand, Gamma globulin has proved effective in the prophylaxis of infections in patients with agammaglobulinemia.[43] Seltzer,[13] Rosenstiel,[56] Kuhns[39] and Bruton[57] have reported improvement in their cases using Gamma globulin alone. Savacool and Landes[59] found Gamma globulin to be helpful in the treatment of a case of acquired agammaglobulinemia. They suggested that Gamma globulin be given only during times when exposure to infections is most likely and rely upon antibiotic prophylaxis at other times. Freundlich[58] reported improvement in a child with agammaglobulinemia using Gamma globulin; however, there was no improvement in an otitis media, and a mastoidectomy had to be performed. Latimer[59] reported cellulitis in one of his patients with agammaglobulinemia which did not respond to therapy until Gamma globulin was added to the therapeutic regimen.

A dose of 0.1 gm. of Gamma globulin per kilogram of body weight intramuscularly every 30 days has given adequate protection to most patients.[1,60] Since Gamma globulin ordinarily is manufactured as a 16 per cent solution, this would represent 0.3 cc. per pound of body weight. In some cases, clinical improvement was not noted below a dosage of 0.15 to 2.0 gm. of Gamma globulin per kilogram of body weight.[1] That the prophylactic dose of Gamma globulin varies in different patients may be due to the fact that Gamma globulin is a heterogenous substance containing many different antibodies which have varying rates of degradation (ranging from 17 to 58 days).[49]

The dosage of Gamma globulin is based on two observa-

tions: *1.* the half-life of injected Gamma globulin in humans ranges between 13 and 32 days,[49] and *2.* a level of 100 to 150 mg. of Gamma globulin per 100 cc. of serum seems to be the minimum necessary to prevent infection, a level easily obtained by the injection of 0.1 gm. per kilogram of body weight.[1,41]

In 1956, the Council on Pharmacy and Chemistry of the American Medical Association approved the use of immune globulin for the treatment of agammaglobulinemia.[61] The Council pointed out that the immunity thus provided is temporary and passive, and emphasized that continued protection depends on routine and regular administration. The Council recommended the deep intramuscular injection of this preparation, preferably in the gluteus.

Although Gamma globulin is apparently the best means of prevention of recurrences of infections in these patients, it has certain disadvantages: *1.* it necessitates the injection of a large volume of Gamma globulin solution at relative frequent intervals which is painful and unpleasant; *2.* continuous replacement therapy presents an economic problem, as Gamma globulin is quite expensive; *3.* it provides only passive immunity; *4.* and, finally, the long term effects of repeated injections of Gamma globulin have not been determined.[41] Because of severe hypotensive reactions, the material cannot be administered intravenously.[41] Chills, fever, myalgia and faintness result from intramuscular injections of over 20 ml.[41] That there is little danger of serum hepatitis, even with prolonged administration, should be emphasized, since the virus of homologous serum jaundice is not associated with the Gamma globulin fraction.[41]

Just how long replacement therapy with Gamma globulin in these patients must be continued is not yet known. So far there has been no report of a patient with agammaglobulinemia resuming the manufacture of Gamma globulin.[60] In some of the patients with secondary agammaglobulinemia (nephrotic, nutritional dysproteinemic) resumption of Gamma globulin production can be expected to accompany recovery from the primary disorder.[60]

Antibiotics have been used successfully in the prophylaxis of infection in these patients. In some instances it may be necessary to supplement Gamma globulin prophylaxis with a program of continuous antibiotic therapy. Zinneman, et al.,[36] reported a case which did not respond to Gamma globulin, but responded to prolonged antibiotic prophylaxis. These workers concluded that prophylactic antibiotic therapy offers advantages over prophylactic Gamma globulin. Mazzitello and Good[43] reported effective prevention of recurrent infections in one case using antibiotics and Gamma globulin, and in several of their patients have used penicillin and tetracylines alternately. Because of the cost involved, a case reported by Zbar, et al.,[62] received no supplemental therapy with Gamma globulin, but was treated with tetracycline alone, and remained free of significant infection for 20 months. Martin, et al.,[63] described an adult case of agammaglobulinemia who required sulfadiazine plus double the usual frequency of Gamma globulin injections for complete protection. Brem and Morton,[27] from the study of seven cases, concluded that the effects of this disease may be ameliorated by the administration of adequate amounts of Gamma globulin and the appropriate use of antibiotics.

Gamma globulin is only as effective as the amount and properties of the specific antibodies in the individual Gamma globulin preparation used.[1] These patients, in spite of Gamma globulin administration, will have the usual respiratory infections suffered by normal individuals; moreover, Gamma globulin and antibiotic prophylaxis will not reverse permanent anatomic changes, such as chronic ear, sinus and lung diseases. Again, this fact emphasizes the importance of proper surgical management of these conditions in patients with agammaglobulinemia.

As has been pointed out, there are definite disadvantages to the use of Gamma globulin; therefore, its indiscriminate use in unproved cases of agammaglobulinemia and in children with recurring respiratory infections should be frowned upon. Turner and Dobson[64] reported good results in the treatment of chronically ill children with repeated respiratory infections using immune globulin. Bernton[65] had gratifying results in

the treatment of children with asthma in preventing upper respiratory infections. On the other hand, Abernathy, et al.,[66] in a double-blind controlled study, found no evidence to support the view that treatment with Gamma globulin has a beneficial effect on infection and the course of chronic asthma in children.

Recently, Good, et al.,[67] reported that transplantation of four lymph nodes from a previously sensitized patient provided immunological reactivity to a patient with acquired agammaglobulinemia that lasted about 75 days. Martin[68] has found by lymph node transplant immunologic capacity lasting up to 160 days. Good, et al., suggested that in light of studies on skin transplantation, a more rewarding response may occur in children with congenital agammaglobulinemia. They recommend the continued consideration of transplantation as a means of correcting the metabolic defect in these patients, and, in addition, suggest as possible approaches to this end, bone-marrow infusion, cancellous bone transplantation and production of splenosis peritonei.

## PROGNOSIS.

The syndrome of agammaglobulinemia is a serious and potentially fatal defect which, if diagnosed and treated, appears to be compatible with normal life.[69] Four of the original 19 patients reported by Gitlin and Janeway have succumbed to infection.[1] The remaining patients have done fairly well, although those with anatomic changes secondary to infection suffer from permanent handicaps. One of three patients described by Hayles, et al.,[70] died of infection, although Gamma globulin was administered regularly. Other cases of death from infection have been reported.[27,40,46,71] There is a great tendency to permanent damage in these patients, and there is a constant danger from infectious disease; thus, diagnosis should be established early and substitution and antibiotic therapy started before irreversible changes occur. Certainly the prognosis in this newly discovered syndrome awaits further years of study.

## HISTORY AND REVIEW OF CASES.

An effort has been made to review a great many of the reported cases of agammaglobulinemia. In the cases described, emphasis has been placed on the symptoms and signs referable to the nose, sinuses, ears, throat and lungs—the areas which are of great interest to one practicing the specialty of otolaryngology.

In 1952, Bruton[44] reported the first case of agammaglobulinemia in a male child as a syndrome of recurrent bacterial infection associated with a lack of Gamma globulin, despite an otherwise relatively normal plasma protein pattern. Prior to this time, several patients with decreased concentration of serum globulin, and in some instances with increased susceptibility to infections had been reported.[72-73] Bruton's[2] patient was an eight-year-old boy who, in four years, had had at least 19 episodes of clinical sepsis, in which some type of pneumococcus was recovered from his blood stream on ten occasions. He was seen initially with a clinical picture of acute osteomyelitis. He had frequent episodes of otitis media and pneumonia. Studies demonstrated that he did not produce antibodies for pneumococcus, diphtheria or typhoid when given specific antigens. Clinical and laboratory studies revealed no deviation from normal until a Tiselius electrophoretic analysis revealed the absence of serum Gamma globulin.

In 1953, Keidan, et al.,[5] reported agammaglobulinemia in a fatal case of generalized vaccinia in a seven-year-old girl. In this same year, Janeway, et al.,[28] were able to confirm Bruton's findings in nine cases. These children had multiple infections, and were unable to produce circulating antibodies. The determination of the absence of serum isohemoagglutinins in patients of blood groups O, A, or B was used as a simple screening test for this condition.

Lowered serum globulins have been observed in patients with edema due to a lowered serum albumin.[76] Hypogammaglobulin has been reported in patients with nephrosis[77] or malnutrition[73] with edema.

Allen[78] treated a middle-aged woman with agammaglobu-

linemia with several hundred plasma transfusions. During this period this patient underwent several successful pregnancies. Zinneman, et al.,[26] reported agammaglobulinemia in two men and one woman who had normal childhood, but who had recurrent respiratory infections, pneumonia, bronchiectasis, and pneumococcic meningitis during early adulthood. In one of these patients the cause of the disease was thought to be secondary to generalized sarcoidosis. The patients were unable to produce humoral bacterial antibodies. Biopsies of the liver, spleen and lymph nodes of one patient showed complete absence of plasma cells, which are thought to be the source of Gamma globulin.

Young and Wolfson[35] reported four men with agammaglobulinemia, three of whom had no lymph node germ centers. All four were extremely susceptible to infection. Arends, et al.,[79] described a 53-year-old woman with agammaglobulinemia who had malignant lymphoma and repeated respiratory and skin infections. Sanford, et al.,[32] described a female adult with no Gamma globulin who had repeated infections of a sprue-like syndrome. Rosecan, et al.,[3] reported two adult male cases of agammaglobulinemia: one experienced repeated upper respiratory infections and diarrhea, and the other only repeated intestinal difficulties.

Prasad and Koza[17] reported the first case of agammaglobulinemia in a female adult. She had a history of recurrent illnesses beginning with sinusitis. She had attacks of pneumonia and meningitis. Clinically, she had lymphadenopathy, hepatomegaly and splenomegaly. Numerous nonspecific granulomata were demonstrated on histologic sections of the spleen and the biopsied axillary lymph node. These workers thought that this finding implicated a disease of the reticuloendothelial system. Prasad and Koza suggested that some infection may have resulted in granuloma formation thereby damaging the reticuloendothelial system and producing agammaglobulinemia.

Wall, et al.,[34] reported two cases of agammaglobulinemia in adults. One patient had repeated bacterial pneumonias and one had repeated infections associated with a sprue-like picture. Of interest is the fact that the first case had a repaired

cleft palate and congenital hip dislocation, as several cases of agammaglobulinemia have been reported in individuals having congenital anomalies.[32] In addition, he had had two episodes of erysipelas. The second case had recurrent episodes of nasopharyngitis, maxillary sinusitis, bronchitis and diarrhea. A lymph node biopsy incision failed to heal for two and one-half months despite vigorous antibiotic therapy.

Seltzer, et al.,[13] reported a case of acquired idiopathic agammaglobulinemia in a 27-year-old male with recurrent upper respiratory infections and pneumonia. They were reasonably convinced that the patient at one time had histoplasmosis and raised the question as to whether histoplasmosis and resulting infection of the antibody-forming reticuloendothelial system could have resulted in permanent depression of antibody formation, or possibly the depressed antibody production made him susceptible to histoplasmosis. From their studies they concluded that the Gamma globulin half-life in idiopathic hypogammaglobulinemia and agammaglobulinemia is normal regardless of the age group.

Young, et al.,[41] described four cases of agammaglobulinemia in male adults. In three cases there was a deficiency in tissue and peripherial blood lymphocytes. An interesting finding was a marked hypergammaglobulinemia in a mother and brother of one case. The first case had a stormy course with frequent infections of purulent otitis media, beginning in childhood, acute mastoiditis, suppurative cervical adenitis, infectious hepatitis, lobar pneumonia and bronchiectasis. At 17 he had an operation for chronic sinusitis and at 18 a lobectomy for bronchiectasis. The other three cases had frequent infections since childhood with bronchopulmonary involvement predominating.

Latimer, et al.,[39] reported a severe wound infection following the surgical excision of a benign breast lesion in an adult female with a proved agammaglobulinemia. The cellulitis responded to therapy only after Gamma globulin administration.

Brem and Morton[27] described their experiences with seven patients in whom Gamma globulin was not demonstrable

electrophoretically. The first three were adults who exhibited the complete pattern of agammaglobulinemia, with absence of antibody production and susceptibility to infection. All three had striking splenic and lymph node enlargement, apparently secondary to agammaglobulinemia or to the resulting infections. Two of them developed advanced liver disease, presumably due to chronic viral hepatitis, possibly of the homologous serum variety. The first patient suffered from sinusitis, otitis media and bronchitis. The second patient had sinusitis, otitis media, mastoiditis, bronchitis and pneumonia. During the course of his infections he had a right and then a left mastoidectomy. His sinuses were surgically drained. The third case had many respiratory infections and bronchiectasis following whooping cough. He had had a bilateral pulmonary lobectomy. The next two cases, a 25-year-old male and a nine-year-old boy, showed marked depression of Gamma globulin electrophoretically, but were able to produce antibodies and were not particularly subject to infection; both had isohemagglutinins. The adult male complained of recurring episodes of abdominal pain with nausea and vomiting. The boy had a peculiar undiagnosed episode of edema lasting about one month. The next two cases were elderly brothers of French descent. They had long histories of upper respiratory infections, bronchitis and pneumonia. Both subsequently developed chronic lymphocytic leukemia. The infections antedated by years the appearance of the leukemias.

Hutchison[71] reported a case of fatal pneumonia in a young child with congenital agammaglobulinemia. The patient's brother had died previously of pneumonia. The writer assumed that since the histologic picture of the lungs in both were similar that both had agammaglobulinemia.

Martin, et al.,[63] described agammaglobulinemia in a 63-year-old woman. She had recurrent upper respiratory infections with sinusitis, tonsillitis and adenitis, oral moniliasis and pleurisy. There was an absence of plasma cells in the bone marrow. She responded only to Gamma globulin and sulfadiazine.

Hinds[69] reported a case of agammaglobulinemia in a 21-year-old male. He had repeated infections. He had laryngitis

and sinusitis, which required antral windows. He had had myringotomies for otitis media. He had episodes of pneumonia, and finally bronchiectasis requiring lobectomy.

O'Brien and Sereda[50] reported agammaglobulinemia in male siblings, ages three and five years. The first child was seen initially because of a painful swollen right ankle, and the second because of a painful left knee. Both patients had a history of repeated respiratory infections, the three-year-old having had severe almost continuous respiratory infections with acute tonsillitis, pharyngitis and acute otitis media, and, finally, pneumonia at 11 months. An uncle on the maternal side died at age five. Autopsy findings suggested that he, too, was afflicted with the disease; thus giving support to the theory that the defect is a recessive sex-linked characteristic similar to hemophilia.

Wechsler and Wolf[51] reported a case of agammaglobulinemia in a 53-year-old female with typical findings of this disease. She had been well until the age of 27. Her illnesses included bronchitis, pneumonia, eyelid infection, meningitis, otitis media and mastoiditis. Because of a persistent otitis media following meningitis, she had a simple mastoidectomy.

Rosenstiel[56] described a case of agammaglobulinemia in a 38-year-old white male veteran of World War II. For many years he had had repeated respiratory infections requiring antibiotic therapy and on many occasions was hospitalized. A review of his past medical history revealed that he had had 20 attacks of pneumonia, one attack of erysipelas, innumerable colds and sore throats, and many attacks of sinusitis requiring surgical drainage.

Congenital agammaglobulinemia in two brothers has been reported by Elphinstone, et al.[52] The first case had bronchopneumonia at the age of two months; left chronic otitis media at the age of three years; left mastoidectomy at the age of seven; and a right mastoidectomy at the age of eight. Mucopurulent material was obtained from antral irrigations. He contracted pulmonary tuberculosis between the ages of seven and eight years. He had repeated episodes of pneumonia.

The second case had empyema, staphylococcal infections of the nose and bronchitis.

Zbar, et al.,[62] reported agammaglobulinemia in a 27-year-old white married housewife who had had ten attacks of pneumonia. A case of primary agammaglobulinemia in a four-year-old male with a history of repeated pyogenic respiratory infections was reported by Sorensen and Partington.[53] He had mild bronchitis at the age of three months; bronchitis and otitis media at seven months; groin abscess at two years; cough and mucopurulent nasal discharge at three years; and pneumonia at the age of four.

Agammaglobulinemia in a 36-year-old male has been reported by Savacool and Landes.[50] At the age of 21 this patient developed prolonged colds, each associated with stuffiness, nasal discharge and general weakness and fatigue. He had two episodes of otitis media lasting about two months. He had chronic sinusitis and recurrent attacks of pneumonia. He had a lobectomy for an unresolved pulmonary infection. He was noted to have splenomegaly and generalized lymphadenopathy.

In 1957, a case of congenital agammaglobulinemia was described by Freundlich[35] in a five-and-a-half-year-old boy who had a Gamma globulin level between 0.5 and 1 mg. per 100 ml. plasma, which was lower than any other case reported in the literature up to that time. The patient underwent an unusually prolonged varicella infection. At the age of one, he had a prolonged case of chickenpox and at one-and-a-half, meningitis. He had episodes of diarrhea and a chronic cough with frequent periods of high temperature. X-rays showed pulmonary changes and sinus disease. An interesting finding was noted, namely, the absence of adenoid tissue in the nasopharynx. He developed a chronic bilateral suppurative otitis media and eventually had a right mastoidectomy. He had recurring bouts of sinusitis.

Martin, et al.,[49] have reported three additional cases of agammaglobulinemia. The first case was that of a 13-year-old Negro male. He had repeated episodes of respiratory infections, pneumonia with empyema and bacteremia, acute

otitis media and bronchitis. In addition, two episodes of septic arthritis occurred. At the time of study, he had moderate bilateral bronchiectasis, chronic pansinusitis, chronic left otitis media and hepatosplenomegaly. The second case was that of a 36-year-old white female who had a history of pneumonia, appendicitis with rupture, sinusitis, bronchitis, pharyngitis and cutaneous furunculosis. While under study, the patient was found to have hepatosplenomegaly, early bilateral bronchiectasis, chronic frontal and maxillary sinusitis, and scattered skin lesions. The third case was that of a 54-year-old white female, who following an episode at the age of 40 years of septic arthritis and bacteremia due to streptococcus pyogenes, developed 11 attacks of pneumonia and bronchopneumonia, staphylococcus septicemia, meningitis and otitis media, generalized herpes zoster, and innumerable episodes of cellulitis, sinusitis, pharyngitis and bronchitis. Studies disclosed severe bilateral bronchiectasis, pansinusitis, and hepatosplenomegaly.

Two additional cases of agammaglobulinemia have been described in adult females by Cooke, et al.[84] Both cases had recurrent pancreatitis and steatorrhea. Citron[40] draws attention to the association of acquired idiopathic agammaglobulinemia with enlargement of the spleen and lymph nodes. He describes two cases and reviews six similar ones in the literature. His two cases had pronounced hepatosplenomegaly and lymph node enlargement. The first case, a 33-year-old man, had a history of gingivitis, laryngitis, pleurisy and pneumonia. The second case, a 17-year-old girl, had a history of pneumonia and had terminal meningitis.

In 1957, Pearce and Parinpanayagam[6] reported the first case of congenital idiopathic hypogammaglobulinemia in a girl in England. The child was three years, eight months of age and had a history of constant infections. Repeated attacks of left otitis media developed into chronic otitis media. She had recurrent attacks of stomatitis, purulent rhinitis and pneumonia. In addition, she had hepatosplenomegaly and palpable cervical lymph nodes. A cervical lymph node exhibited the characteristic feature of absence of plasma cells.

Kuhns and Solow[39] reported the occurrence of little or no

Gamma globulin in a 19-year-old female patient with a long history of susceptibility to infections with other long-standing abnormalities, most of them related to bones or skin. She had recurrent urinary infections and upper respiratory infections. She had frequent colds and a clogged nose, and she became a mouth-breather at an early age. She had a chronic cough. X-rays showed a chronic hyperplastic pansinusitis. She had a crooked spine; one leg was shorter than the other; and she had a slight bilateral hallux valgus deformity. The skin of her body showed numerous areas of depigmentation.

Barrett and Volwiler[9] described a case of acquired agammaglobulinemia in a husky 19-year-old sailor, and a case of secondary agammaglobulinemia in a 67-year-old male suffering from multiple myeloma. The sailor had two episodes of pneumonia within two months, but had no previous history of susceptibility to infection. His Gamma globulin levels were on the borderline between safe and dangerous hypogammaglobulinemia. The elder patient concurrently developed multiple myeloma and extreme susceptibility to infection. In this case the question was raised as to whether the loss of antibody production or of leukocyte production, or the failure of some other defense mechanism was responsible for the recurring infections.

A case of agammaglobulinemia in a 53-year-old housewife has been reported by Domz and Dickson.[60] The interesting aspect of this case is that she had repeated attacks of pneumonia, despite antibiotic and Gamma globulin prophylaxis.

Zelman and Lewin[37] describe a case of adult agammaglobulinemia with multiple congenital anomalies. Clinically this patient had recurring pyogenic infections, a sprue-like syndrome, and reticuloendothelial hyperplasia of the spleen and lymph nodes with granuloma formation. This association suggests the possibility that such adult "acquired" agammaglobulinemia may, in fact, represent another congenital anomaly. A hereditary basis is suggested by the presence of hypergammaglobulinemia in both parents of this patient.

## CASE REPORTS.

*Case 1.* The patient was an eight-year-old white girl, who was admitted

to the hospital because of a persistent left otitis media and the sudden appearance of swelling and tenderness of the left knee and right wrist. She had a history of recurrent occurrences of respiratory infections since earliest childhood. For several months she had had purulent drainage from the left ear which had failed to respond to the usual measures, including intensive antibiotic administration and radium therapy to the nasopharynx. For several years she had suffered recurrent ear infections and purulent sinusitis. She had a chronic productive cough.

She was normal at birth; however, at the age of four weeks she had an upper respiratory infection with a temperature of 103.8° F., which responded satisfactorily to intramuscular penicillin. At the age of two, she was seen many times by her family doctor for upper respiratory infections. On one of these occasions, when she had acute bronchitis and otitis media, an axillary temperature of 106° F. and rather prolonged febrile convulsions were recorded. Of interest is the fact that at the age of five she had chickenpox with secondary infection requiring intramuscular penicillin and aureomycin ointment locally. When she had the smallpox vaccination, she had a secondary reaction on the right eyelid.

At the age of six, she had many upper respiratory infections with a "stuffy nose" and discharge. This same year, she had several episodes of otitis media and pneumonia. Because of the persistent infections, arrangements were made for her to have a tonsillectomy and adenoidectomy. A significant observation was made at the time of surgery, namely, the complete absence of adenoid tissue. Her tonsils were slightly enlarged, septic and because of adhesions had to be removed by dissection.

Early in 1955, at the age of seven, she was seen many times by her family physician with ear, nose, throat and lung infections. For the first time, splenomegaly was noted. X-rays of the chest, made in March of this year, showed pneumonitic changes in the central and mesial lung fields which did not completely resolve. In the Spring of this year she was hospitalized by a pediatrician in a neighboring city. He reported to the family that all tests were negative; however, he gave her two transfusions, after which she showed a great deal of improvement, and, consequently, was not seen by her family physician from April, 1955, until February, 1956. From this time until her admission to the hospital she was treated for many episodes of bronchitis, purulent sinusitis and otitis media.

Physical examination revealed the following findings: temperature 98.6° F., pulse 100, respirations 20, blood pressure 100/60. The patient appeared slightly anemic, but was not in acute distress. Her weight was 55 pounds. The pupils were round and equal and reacted to light and accommodation. The nasal membranes were moderately congested, and a purulent drainage was present. The maxillary sinuses were cloudy to transillumination. The right ear drum was retracted and scarred. A profuse, sticky discharge was noted to be exuding from a central perforation in the left ear drum. No mastoid tenderness was present. The tonsils were absent and the fossae clear. A thick postnasal drainage was noted. On palpation of the neck several small non-tender lymph glands were noted bilaterally. The lungs were clear. The heart sounds were normal. Examination of the abdomen revealed rather marked splenomegaly. There was slight swelling and tenderness of the left knee and right wrist.

Laboratory examination revealed the following findings: urine negative; hemoglobin 10.5 gm.; white blood cell count 4,200 with normal differential. Erythrocyte sedimentation rate was 12 millimeters in one hour. Serology negative; normal prothrombin time; fibrinogen normal; clot retraction two hours; prothrombin consumption 38 per cent; platelets 222,000. The antistreptolysin titer was negative. No L-E cells were

found. All agglutinations were negative. A culture from the left ear revealed a pseudomonas aeruginosa and hemolytic staphylococcus which were not sensitive to any antibiotics. Alpha streptococci and Gram negative diplococci, which were highly sensitive to a number of antibiotics, were cultured from the throat. An electrocardiogram was normal. A bone marrow examination was reported as showing slight hyperplasia with increase in the percentage of nucleated red cells. A chest X-ray showed extensive changes in both lung fields with a large amount of increased density radiating out from the hilar regions. A lateral soft tissue film showed no lymphoid tissue in the nasopharynx. Sinus X-rays showed clouding of all of the paranasal sinuses. X-rays of the right wrist were normal, except for slight soft tissue swelling. Skull films showed stippled punctate calcium deposits in the skull in the region of the choroid plexus bilaterally. Films of the mastoids showed very poor cell development bilaterally with sclerosis present, but no evidence of cell break down or bone destruction.

Other laboratory findings were as follows: total serum proteins were 4.9 gms. per 100 cubic centimeters, of which albumin was 4.9 and globulin 1.1 gms. The A/G ratio was 4.5/1. Serum electrophoresis showed the total protein to be markedly decreased, 5.2 gms. per 100 cc. (normal 7.35 gm. per 100 cc.). There was a complete absence of Gamma globulin. By the immunochemical method she was shown to have a serum Gamma globulin level of 100 mg. per 100 cc.* There was a relative increase of the albumin fraction—72.0 per cent (normal 59.4 per cent). The patient was found to be in blood group O, Rh positive. There were no anti-B isohemagglutinins and only very weak isohemagglutinins demonstrated in her serum.

A diagnosis of agammaglobulinemia was made and the intramuscular administration of Gamma globulin was begun, the patient receiving 16 cc. as an initial dose. The symptoms relative to the wrist and knee disappeared in several days following admission to the hospital. In spite of intense antibiotic therapy, the drainage from the left ear persisted; consequently, a complete simple mastoidectomy was performed. Her postoperative course was uneventful, and she was discharged 11 days following surgery on Dec. 11, 1956, in good condition, with a dry left ear. Since this hospital admission, she has received 10 cc. of Gamma globulin bi-monthly. In addition, she has been maintained on prophylactic doses of penicillin.

For the next six months the patient did well generally, except for a chronic maxillary sinusitis. At the age of nine, in July, 1957, bilateral antral windows were made. Much pus and hyperplastic tissue were removed from each maxillary sinus. In November of the same year, she was admitted to the hospital for treatment of otitis media and bronchitis. A chest X-ray showed progression of the infiltrative changes in both lungs. With this admission she had a leukopenia, the white blood cell count being 3,000. Serum protein analysis revealed a total serum protein of 5.4 gm. per 100 cc. and a Gamma globulin of 2.5 per cent (practically absent). The drainage from her ears cleared promptly and the bronchitis improved on chloromycetin therapy.

For the past ten months the patient has done very well as far as her sinuses and ears are concerned; however, at the time of her last admission in July, 1958, her pulmonary symptoms had shown no improvement. Her nasal membranes were normal; no pus was present in her nose; and there was no postnasal drainage. Her maxillary sinuses were clear to transillumination. Small central perforations were present in both

*Dr. David Gitlin, Children's Hospital, Boston, Mass., kindly performed this test.

ear drums, but no drainage was present. An interesting observation was that in the past year, intermittently, she has had painful, feverish swelling of her knees, wrists, shoulders and hips. These symptoms subside spontaneously in about five days. Serum electrophoresis revealed a total protein of 5.6 gm. per 100 cc., and a serum Gamma globulin of 3.8 per cent. The zinc sulfate turbidity test was reported as being 0.25 units (values of 0 to 1 unit are compatible with agammaglobulinemia). The sweat test was negative. A chest X-ray showed further progression of the pulmonary changes. A chest consultant advised against definitive procedures on the lungs, as he felt that if the changes were those of bronchiectasis they were almost surely widespread and not amenable to any but general measures. Electrophoretic studies revealed normal serum proteins in all of the members of her family, except for her father whose Gamma globulin was in the lower limits of normal.

*Case 2.* The patient was a four-year-old white boy, who was admitted to the hospital Jan. 20, 1958, for a tonsillectomy and adenoidectomy. He had suffered from repeated ear and upper respiratory infections, and his mother stated that he kept a "stuffy" nose through the Winter months. He was small and underweight. For about two months he had had a left otitis media, the drainage having ceased about one week prior to this admission.

He was born at home and was premature, weighing four pounds at birth. At the age of two weeks he was hospitalized with pneumonia. His temperature went up to 107° F., and he had convulsions for five days. After six weeks in the hospital, he was discharged, weighing five pounds and eight ounces. At the age of six months he was again admitted to the hospital with a temperature of 104° F. He cried continuously during his eight-day stay,, and his mother was told that he was being treated for "gas on the stomach." At the age of 15 months, he was treated at home for pneumonia.

His present family physician saw him for the first time at the age of 18 months. His history mentions the fact that up to this time he had had about ten episodes of acute purulent otitis media. He weighed 19 pounds and three ounces, and his hemoglobin was 6.5 gm. The anemia was apparently nutritional, as it responded satisfactorily to iron therapy. His mother states that he had "three day measles" (Rubella) at the age of two.

At the age of 27 months, in January, 1956, he was hospitalized briefly for gastroenteritis, bronchitis and otitis media. A urinalysis was normal. His hemoglobin was 14.5 gm. and his white blood cell count was 8,050. A chest X-ray was negative.

For the next two years he was taken to a pediatrician and his family doctor on many occasions because of poor appetite, failure to gain weight and repeated colds and ear infections. During this period he had seven recorded episodes of otitis media.

Physical examination revealed the following findings: temperature 98.6° F., pulse 80, and respirations 20. The patient appeared small for his age and undernourished. His weight was 34 pounds. The pupils were round, equal and reacted to light and accommodation. The nasal membranes were moderately congested. The maxillary sinuses were cloudy to transillumination. A central perforation, measuring 2 mm. by 1 mm., was present in the left ear drum. No discharge was present. The tonsils were small, fibrotic and imbedded. The adenoids were not visualized, but on palpation were thought to be small. A few small non-tender lymph glands were palpated in the superior cervical areas on each side. The lungs were clear and the heart sounds normal.

Laboratory examination revealed the following findings: urine negative; hemoglobin 13 gms.; white blood cell count 9,900, with a normal differential; bleeding time two-and-a-half minutes; and coagulation time ten minutes.

At operation the tonsils were found to be small, fibrotic and many adhesions were present. Only a minimal amount of adenoid tissue was present in the nasopharynx. The microscopic examination of the tonsils was reported as follows: "The tonsils are covered in part by a benign stratified squamous epithelium, but the greater portion of the epithelium is missing. No significant exudate is present within the crypts. The lymphatic tissue does not appear significantly hyperplastic." The patient did well following surgery, and was discharged on his first postoperative day.

Because of the paucity of adenoid and tonsil tissue and the clinical history of recurrent ear and respiratory infections, agammaglobulinemia was suspected. After recuperating from the tonsil surgery, further studies were done. By the paper electrophoretic technique, the total protein was slightly decreased, 6.2 gms. per 100 cc., of which albumin was 4.3 gms. and globulin 1.9 gms. The Gamma globulin was 6.9 per cent (normal 14.4 per cent). There was a relative increase of the albumin fraction—69.4 per cent (normal 59.4 per cent).

These studies indicated an abnormality of the serum proteins and a very low Gamma globulin. Although a definite diagnosis of agammaglobulinemia could not be established, because of the clinical history administration of 8 cc. of Gamma globulin each month was started in March, 1958. At this time X-rays of his sinuses, lungs and mastoids were made. The maxillary sinuses were almost completely opaque. The lung fields were clear, and the heart, aorta and mediastinum were normal. The mastoids were normally aerated and showed no definite evidence of infection.

For the last six months the patient has done well, except for an occasional attack of sinusitis. The left ear has remained dry, but the drum perforation has not healed.

Additional laboratory studies were done in August, 1958. The total serum protein by chemical analysis was 6.4 gm. per 100 cc., of which albumin was 4.65 gm. and globulin 1.75 gm. By serum electrophoresis the Gamma globulin was shown to be 1.9 per cent (normal 12.2 per cent), which was much less than the initial determination of 6.9 per cent, despite Gamma globulin administration. The patient was found to be in blood group O, Rh positive. Only very weak anti-A and anti-B isohemagglutinins were demonstrated in his serum; his anti-A isohemagglutinin titer was 1:1 and his anti-B titer was 1:4. The zinc sulfate turbidity test was reported as being 0.25 units (values of 0 to 1 unit are compatible with agammaglobulinemia). These tests confirmed the diagnosis of agammaglobulinemia.

## COMMENT.

Cases of agammaglobulinemia in a young girl and a young boy have been reported, exhibiting the complete pattern of this syndrome. The repeated infections in these patients must be attributed to their deficiency of Gamma globulin and concomitant poor antibody response.

The initial examination of the serum of the first case by paper electrophoresis showed a complete absence of Gamma globulin. After the administration of Gamma globulin, subsequent electrophoretic studies revealed small quantities of this serum component. The first examination of the serum of the second case showed a Gamma globulin level of 6.9 per cent, which was not considered low enough to be considered diagnostic of agammaglobulinemia. In spite of Gamma globulin administration, serum electrophoresis six months later showed the Gamma globulin to be almost completely absent. A diagnosis of agammaglobulinemia was then confirmed.

Both of these patients demonstrated weak or absent isohemagglutinins. The zinc sulfate turbidity test in each case was compatible with agammaglobulinemia.

Although the girl has had repeated and varied bacterial infections, she apparently has developed immunity to the common viral infections, which is characteristic of this syndrome. The boy has had only Rubella, and so far has escaped the common acute infectious viral diseases of childhood so that his ability to develop immunity to viruses has not been tested.

Of course, the striking feature in these patients is the occurrence of repeated infections of the nose, sinuses, ears, throat and lungs, the diseases which lie within the field of the otolaryngologist.

The absence of adenoid tissue in a four and a six-year-old child with repeated respiratory infections is a most unusual finding; consequently, when one discovers very little or an absence of lymphoid tissue in the nasopharynx of a child, agammaglobulinemia should be strongly suspected.

The first patient has splenomegaly and lymph node enlargement implying disease of the reticuloendothelial system, which is a common finding in this disease. On two occasions she has had neutropenia and never responded with leukocytosis to acute infection. Granulocytopenia during infection has been reported in several patients with agammaglobulinemia.[3] One patient was regarded for years as having recurrent splenic neutropenia before the diagnosis of agamma-

globulinemia was made[3] This patient has had the polyarthritis which has occurred in about one-fourth of the reported cases. The second case has had very minimal lymph node enlargement, but no splenomegaly, neutropenia, or polyarthritis.

In spite of Gamma globulin administration and penicillin prophylaxis, the time-honored surgical procedures of the otolaryngologist were necessary to eradicate ear and sinus disease in the first case. The progression of the pulmonary changes despite Gamma globulin administration, antibiotic prophylaxis and surgical correction of sinus and ear disease should also be emphasized.

The first case, a girl, is believed to represent acquired agammaglobulinemia, although the onset of infections shortly after birth would lend support to a diagnosis of the congenital type. The advanced pulmonary pathology is more commonly described in the acquired type. Her sex is in favor of the acquired type, since congenital agammaglobulinemia is supposed to occur only in males. A few cases have been reported in females,[6,15] and statistically there is a rare chance of this happening.[1] The second case, a boy, is thought to represent the congenital type.

The writer has two additional cases with very low Gamma globulin levels under observation. Both of these patients have chronic ear and mastoid disease. Perhaps all patients with recurring and chronic ear and mastoid infections should have electrophoretic serum studies as has been recommended for all cases of bronchiectasis.[43,85]

## SUMMARY AND CONCLUSIONS.

*1.* The disease entity agammaglobulinemia has been described in detail and the literature reviewed.

*2.* Typical cases of acquired agammaglobulinemia in a young girl, and congenital agammaglobulinemia in a young boy have been reported. The possibility of the disease in the girl being of the congenital type has been discussed.

*3.* Six years of case reports and study by competent workers

has greatly widened our knowledge of an unusual and important syndrome.

*4.* The otolaryngologist often has the first opportunity to make the diagnosis of agammaglobulinemia, whether it is the congenital or the acquired type. He should strongly consider this diagnosis in any patient with recurring acute or chronic infections of the respiratory tract. He should also think of this diagnosis in any patient showing a striking deficiency or absence of adenoid tissue.

*5.* Paper electrophoresis of the serum proteins, which is now generally available, will usually establish the diagnosis. Other presumptive clinical, laboratory and X-ray findings have been reviewed.

*6.* As agammaglobulinemia is closely tied up with the immunologic mechanisms, there are many unsolved problems in medicine whose nature may be clarified with further study of this disease, particularly in the field of protein metabolism and resistance to infection.

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209 Medical Arts Bldg.

# CYTOMEGALIC INCLUSION DISEASE OF THE NOSE.*

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Cytomegalic inclusion disease, or generalized salivary gland virus infection, is ordinarily thought of as a multisystem virus disease occurring mainly in children and stillborn infants; however, it can manifest itself in organs of interest to the otolaryngologist. It is the purpose of this thesis to aid in the diagnosis and elucidation of an occasional unusual salivary gland or nasal disease. The disease has been characterized by "owl-eyed" giant cells with nuclear and cytoplasmic inclusions. The cells are seen in the epithelium of various viscera and the cerebrum. Although such cells had been described as long ago as 1904 by Jesionek and Kialemanoglou,[1] who observed them in kidneys of a stillborn infant, it is only recently that the disease has been recognized as an entity of some importance which can occur in any age group in a mild localized form or a fatal disseminated type. Following the original work, Ribbert[2] reported the same inclusions occurring in a newborn infant and in the salivary glands of two older children. The term "cytomegalic" was suggested first by Goodpasture[13] to differentiate this entity from other inclusion diseases. Since then, numerous reports of this disease have appeared in the literature. The cases described were usually diagnosed at autopsy. Smith and Velios[5] reviewed the literature comprehensively in 1950. They found 69 cases and added 20 previously unreported cases. Medearis[20] has presented an excellent review of 132 cases.

The characteristic large and pathognomonic mononuclear cell, upon which the diagnosis is usually based, has been well described by Cappell and McFarland,[3] and by Watt, Saxton, and Lee.[4] This large cell is usually epithelial, and rarely mesenchymal or endothelial. It is considered by most pathol-

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ogists to be easily recognized and distinct from other diseases with intracellular inclusions. The extraordinary size of the cell, up to 35 microns, and the deeply staining acidophilic or purplish nuclear inclusion with a surrounding clear halo extending to the nuclear membrane are characteristic. The nuclear membrane is distinct, and near it are dark chromatin masses of different sizes. The cytoplasm is abundant and either acidophilic or amphophilic. In it are basophilic inclusions which usually arrange themselves in a crescentric pattern near the periphery.

The etiology of the disease is considered by most investigators to be a virus, related to the salivary gland virus found in laboratory animals, because the cytoplasmic and intranuclear inclusions characteristic of cytomegalic disease are similar to inclusions found in other human and animal disease of known virus etiology. There is evidence of species specificity of the virus, because to date, there has been no reported successful transfer of the disease to animals; however, this is to be expected, since the salivary gland inclusion disease occurring in rodents and other animals has been found to be species specific.[6] This isolated filterable virus, apparently of low virulence in the rodents, was capable of transmitting the disease to other animals, with intranuclear inclusions found at the site of injection, and salivary glands. At times, a generalized infection was produced with pathological changes in the lungs, abdominal organs, and brain.[5] This appears to be analogous to the situation described in man. Weller[19] has isolated the virus from liver biopsies (showing cytomegalic inclusions) and from the urine of children with cytomegalic inclusion disease, propagated it in human fibroblasts and produced *in vitro* cellular changes with nuclear inclusions. Rowe[21] and Smith[22] have isolated from human tissuse the filterable virus capable of producing the typical cytopathological inclusions of this disease. The virus also produced complement-fixing and neutralizing antibodies with species specificity. The presence of antibodies to the virus in a high percentage of the population indicates that it is of wide distribution; therefore, it exists in a latent or asymptomatic form. The virus has been further described and studied by filtration and the electron microscope.[16]

In man, the salivary gland virus infection is often transmitted from an asymptomatic mother to her fetus. The newborn infant may appear healthy but have a latent infection with salivary gland involvement; or the fetus may have a disseminated infection apparently because of greater susceptibility of fetal tissues.[5] Debility of the child or adult by a concomitant disease, such as avitaminosis, is felt to predispose to generalized infection. Fatal generalized infection most often occurs in the first several years of life.

Pathologically, in man, various systems and organs are involved. There is epithelial involvement of the salivary glands, alveoli, and bronchi of the respiratory tract, the tubular epithelium of the kidney, liver, and gastrointestinal tract. The brain, eye, pancreas, and adrenal glands are less commonly involved. Apparently the organs may be involved individually or in any combination. In addition to the large incision-bearing mononuclear cell, the histological picture shows infiltration of lymphocytes and macrophages, a fibroblastic reaction, and occasionally necrosis.

In the kidney there is a focal interstitial nephritis and tubular dilatation with desquamation. The nephrosis or nephritis produced is rarely severe. Because of the renal tubular involvement with exfoliation of cells into the urinary tract, Wyatt,[4] in 1950, first suggested the use of urinalysis and identification of the characteristic cytomegalic cell as a diagnostic aid. Actual demonstration of the cell in cytologic preparations of urine sediment was not made until 1951 by Fetterman,[9] and later by Mercer.[8] Chronic or interstitial pneumonitis is one of the most frequent manifestations. Pulmonary cysts, atelectasis, and necrosis have been reported.[11,14] The alveolar cells are swollen and many contain inclusions and have desquamated into the lumen with a protein coagulum.[12] In the brain, focal areas of encephalitis with mononuclear infiltration with intranuclear inclusions have been found in ganglia, glial cells, and also meninges. Necrosis and hemorrhage in the basal ganglia, hydrocephalus, and diffuse intracranial calcifications have also been seen. Liver damage results from periportal inflammation, necrosis, biliary obstruction, and fibrosis. Inclusions in the cord and bile duct

cells, leukocytic infiltration, and accumulation of fat in the parenchymal cells has been seen.[12] Biliary cirrhosis has been reported. A blood dyscrasia is a rather frequent finding in infants with some of the following manifestations: purpura, splenomegaly, anemia, petechiae, thrombocytopenia, hemorrhage, and extramedullary blood formation. The large and small intestine have at times shown infiltration with cytomegalic cells and ulceration. Ocular pathologic changes have been uveitis, cataract, and retinal infiltration with inclusion cells.

Inclusion disease in the salivary glands and pancreas has been rather frequently reported with cellular infiltration, interstitial fibrosis, and small foci of necrosis. As yet, there has been no correlation with newer concepts of salivary gland disease, brought about by refinements in sialographic technique.[10] One may only speculate what relationship exists between non-obstructive sialectasis, Mikulicz's disease, "chronic asymptomatic enlargement," and cytomegalic inclusion sialadenitis.

In the diagnosis of cytomegalic inclusion disease there has been confusion with syphilis, toxoplasmosis, hemolytic disease of the newborn, sepsis, measles, and serum hepatitis. The differential diagnosis from most of these diseases is made by the appropriate blood test. The disease pattern and resulting clinical picture varies widely with the type of involvement. It may be either an acute or chronic, occasionally febrile disease, which may feature interstitial pneumonitis, nephrosis, cirrhosis, blood dyscrasia, or central nervous system manifestations. The signs and symptoms may include fever and weight loss, dyspnea, cough, jaundice, hepatomegaly, and splenomegaly, purpura, petechiae, hemorrhage, mental and motor retardation, vomiting and diarrhea. Skull X-rays may show diffuse calcifications outlining the ventricles. Liver and lung biopsies have been successfully used for diagnosis.[12] The less traumatic examination of body fluids seems to have more promise. The diagnosis may be confirmed by identification of the inclusion-bearing cell in stained smears of urinary sediment, salivary and bronchial secretions, or gastric washings.[24] The smears are fixed on slides in equal parts of

ether and 95 per cent ethyl alcohol for 20 minutes, then stained with hemotoxylin and eosin or Wright's stain. A negative test does not invalidate the diagnosis.

The treatment is mainly symptomatic, since there is no specific vaccine and a specific anti-viral therapeutic agent is unavailable. Birdsong[15] feels that there is a rationale and evidence to support the use of Cortisone, and that in infants exchange transfusion may be valuable. Gamma globulin for its antibodies and antibiotics may be used in addition to supportive therapy; also of value is the occasional removal of diseased tissue, as will be seen in the following patient who typifies an apparent localized disease.

Mrs. J. J., a 56-year-old, colored schoolteacher, was first seen Oct. 9, 1954, complaining of a burning sensation in her nose of two months' duration. There was also frequent sneezing, bloody and yellow thin drainage, and nocturnal nasal obstruction. Examination revealed erythematous, crusted, and weeping lesions of the nasal vestibule. The nasal mucosa appeared about normal in color but was slightly swollen and the surface granular. The remainder of the examination was not unusual. A diagnosis of non-specific nasal vestibulitis was entertained and the patient was instructed in the topical application of a neomycin and bacitracin ointment. Routine X-ray examination of the paranasal sinuses was negative. She did not keep her next appointment, and was not seen again until January 29, 1957, at which time she stated she had progressive nasal obstruction and continued rhinorrhea. Examination revealed the nasal vestibulitis again, but now the nasal chambers were filled by pale hyperplastic mucosal changes. The appearance differed from that of the allergic nose with polyps in that the lesions varied in size, but were generally smaller than allergic polyps, and arose from the entire lateral wall as well as the septum. Although the larger growths had a smoother surface, the smaller ones appeared nodular or papillary.

On Feb. 24, 1957, she was admitted to the hospital, where she gave a history as above and that she had constant obstruction of the left nostril for the past year and frequent "colds." She complained of mild exertional dyspnea and occasional precordial pain. She had previously been treated for hypertension and nervousness. She denied having a cough, bronchial sputum, ankle edema, weight loss, jaundice, or melena. There was nocturia one or two times. Her only operation had been a hysterectomy and bilateral salpingo-oophorectomy in 1945. She had two pregnancies and had borne two children, who were living and well. There was no known history of allergy, either personally, or in her family. Except for the rhinological findings, a blood pressure of 180/93, and on retinoscopy, vasospasm and arteriovenous nicking, the physical examination was not remarkable. The liver and spleen were not palpable.

Examination of the blood revealed 12.6 grams of hemoglobin, red blood cell count of 4.48 mil/mm$^3$., hematocrit 39 per cent. The white blood cell count was 9,350 with 55 segmented polymorphonuclear leukocytes, six monocytes, and one eosinophil.

On Feb. 25, 1957, under local anesthesia, an extensive intranasal removal of these lesions was carried out without difficulty, except for greater bleeding than was expected. The pathological report is as follows:

"Grossly the specimen consists of multiple pieces of edematous soft membrane which in some areas is almost translucent. The membranes together form a mass measuring 5x4x.5 cm. Multiple small polypoid nodules arise from the surface of the membrane. On microscopic examination the sections consist of a papillary and polypoid structure, which is lined by pseudostratified columnar epithelium, showing areas of squamous metaplasia and transitional type of epithelium. The papillary projections consist of moderately edematous stroma containing dilated blood vessels and lymphatics and showing marked infiltration of lymphocytes, and in some areas, occasional neutrophiles. The epithelium is everywhere well demarcated from the stroma by a fairly distinct basement membrane. In the epithelium are many large cells with nuclear inclusions surrounded by a clear halo (see Fig. 1). There are remnants

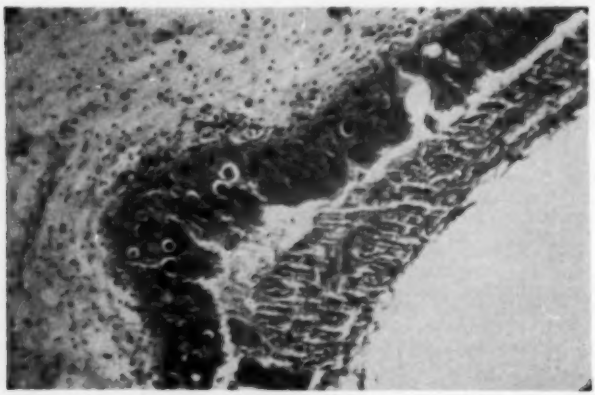

Fig. 1. One can see a number of cytomegalic cells in epithelium with the submucosal reaction.

of nuclear material at the periphery contained by a very distinct and sharp nuclear membrane. In the more advanced lesions the epithelial cells appear distended by large inclusion bodies which are sharply outlined, round, and show moderate variation in size. The inclusion bodies are much larger than ordinary cells and sometimes only an outline of the cell membrane and nucleus is recognizable (see Fig. 2). In the more advanced lesions, apparently the entire cell is destroyed by the inclusion body. The diagnosis was cytomegalic inclusion disease.

Postoperatively she received penicillin for several days. Except for a nodular recurrence on the left inferior turbinate a month later, the nose cleared remarkably well. Six months postoperatively there was a recurrence of the vestibulitis, lasting two weeks. A year-and-a-half postoperatively she was asymptomatic. Examination of the nose revealed only a mild pale granular hyperplastic mucosal change of the middle turbinates.

Complete blood count was as follows: hemoglobin 12.2 gm., or 84 per cent; red blood cells 4.6 million, micro hematocrit 39, white blood cell count, 8,150, with 45 polymorphonuclear leukocytes, 49 lymphocytes, five

monocytes, and one stab. The urinalysis revealed numerous epithelial cells but none with inclusion bodies, occasional granular casts, three to five white blood cells, and an occasional red blood cell per high power field. A trace of occult blood was found in the urine. One might wonder whether early renal cytomegalic disease were developing.

## SUMMARY.

The history of cytomegalic inclusion disease has been traced since the finding of an unique cell in 1904. Laboratory and research work establishing the etiologic agent as the salivary gland virus has been reviewed. Our present knowledge of the

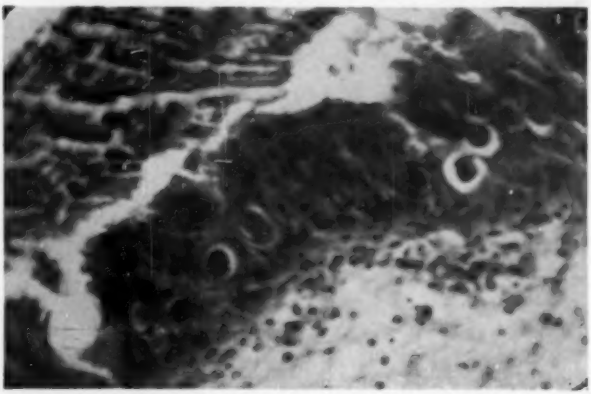

Fig. 2. High power magnification showing the dark nuclear inclusion with the surrounding clear halo.

epidemiology of the disease is not complete. Cellular and organ pathology has been tabulated. The clinical picture, differential diagnosis, diagnostic tests, and treatment were outlined.

In conclusion, evidence has been presented of the existence of an unusual specific virus disease entity which may infect the nasal or other respiratory passages, or the salivary glands. When confronted by a patient with unusual hyperplastic and obstructive nasal mucosal changes, cough, or unexplained salivary gland disease, cytomegalic inclusion disease should be considered and excluded by a careful history and system

review, general physical examination, laboratory studies with examination of stained fresh nasal and salivary gland secretions, and the urinary sediment for the diagnostic cell.

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## OTOLOGICAL FUNCTIONAL MICRO-SURGERY POST GRADUATE COURSE.

A practical course of surgical techniques in otological surgery will be conducted by Dr. Michel Portmann at the University of Bordeaux, France, Ear, Nose and Throat Department, June 26 to July 5, 1960. This course will be given in English.

The number of assistants will be limited to twenty, divided into two groups. The fee of $100.00 is to be paid at the Faculty of Medicine of Bordeaux, at the beginning of the course. Applications should be sent to Dr. Michel Portmann, 45 Cours Foch, Bordeaux, France.

# MULTIPLE NEUROFIBROMATOSIS INVOLVING THE LARYNX.

EUGENE L. YURICH, M.D.,
and
G. JAN BEEKHUIS, M.D.,*
Madison, Wis.

## INTRODUCTION.

Multiple neurofibromatosis was classically described by von Recklinghausen in 1882. It is known mainly to dermatologists because of the typical skin manifestations of multiple cutaneous tumors and "cafe-au-lait" spots. In addition, these tumors may be found to involve the viscera and the central nervous system. There may also be associated malformation of bone and mental disturbances of the deficiency type.

In order to avoid a confusion in terminology, one might best refer to this disease entity as multiple neurofibromatosis, or "von Reckinghausen's disease of the nervous system."[1] In so doing, one would differentiate it from von Recklinghausen's disease of bone (generalized osteitis fibrosa cystica).

Crowe and his associates[2] in 1956, while reviewing 227 cases over a 16 year period, found the incidence of this disease to be one per 2,500-3,300 births. Despite his relative frequency, concomitant involvement of the larynx has been extremely rare.

## REVIEW OF THE LITERATURE.

In reviewing the literature, we found eight previously reported cases of multiple neurofibromatosis with associated involvement of the larynx. In one of these as reported by Hoover,[3] there were no skin manifestations; however, as reported by one author,[1] neither cutaneous tumors nor "cafe-au-lait" spots need be present to establish the diagnosis.

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| Author | Age | Sex | Site | Treatment | Comment |
|---|---|---|---|---|---|
| Colledge[4] 1930 | 44 | F | Right Aryepiglottic Fold and Pyriform Sinus | Lateral Thyrotomy | Symptoms of Hoarseness and Dysphagia. |
| Hoover[1] 1940 | Teens | F | Right False Cord and Aryepiglottic Fold. | Thyrotomy | Lesions of Pharynx, Retrotracheal Area and Mediastinum but No Skin Lesions. |
| Helg[5] 1950 | 7 | F | False Cord and Aryepiglottic Fold | Tracheotomy and Thyrotomy | |
| Holinger and Cohen[6] 1950 | 27 | M | Left Pyriform Sinus | Removed with Snare Forceps | Pedunculated, Very Vascular Tumor; Dyspnea and Dysphagia. |
| Figi and Stark[7] 1953 | 41 | M | Both Arytenoids, Aryeppiglottic Folds, and Retrocricoid | Biopsy | Hoarseness. |
| Figi and Stark[7] 1953 | 50 | F | Left Arytenoid and Retrocricoid | Cutting Diathermy Under Suspension Laryngoscopy | Hoarseness. |
| Gibbs, Taylor and Young[8] 1957 | 3 mo. | M | Retrocricoid | Tracheotomy | Progressive Stridor. |
| Burgdorf[9] 1954 | 17 | F | Retrocricoid | Biopsy | Dysphagia. |

Fig. 1.

The reported cases and pertinent data are demonstrated in the following chart (see Fig. 1). We have purposely omitted cases of solitary neurofibroma of the larynx in our review.

## PATHOLOGY.

In multiple neurofibromatosis, there appears to be a distinct hereditary factor present, with several persons in one family at times being affected. There is an increased incidence of other congenital malformations and a greater tendency toward the development of pheochromacytoma of the

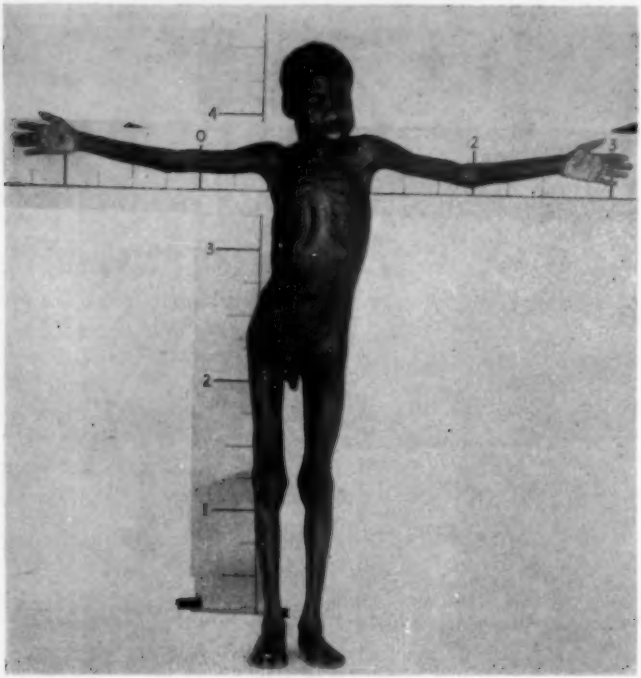


Fig. 2. The patient demonstrates shortness in stature and obvious bone deformities.

adrenal gland.[1,10] Harrison[10] states that 5 per cent of patients with pheochromacytoma have associated neurofibromatosis.

Grossly, the tumor involving the larynx may or may not be encapsulated, with a greater tendency toward poor encapsulation in multiple neurofibromatosis as compared to the usual well encapsulated solitary neurofibroma. The tumor apparently grows along the nerve trunk and the common sites of laryngeal involvement are the arytenoids and the aryepiglottic folds.

Although the histologic appearance includes both neural (ectodermal) and connective tissue (mesodermal) elements,

it is now generally accepted to be neuroectodermal in origin. The tumor arises from the Schwann cells which sheathe all the nerve fibers outside the central nervous system.

These tumors are usually benign and become clinically significant when encroaching on vital structures. Helg[5] disputes the possibility of malignant degeneration and recurrence following removal. Harrison[10] feels that 5 to 10 per cent of neurofibromata may undergo malignant change. Burgdorf[9]

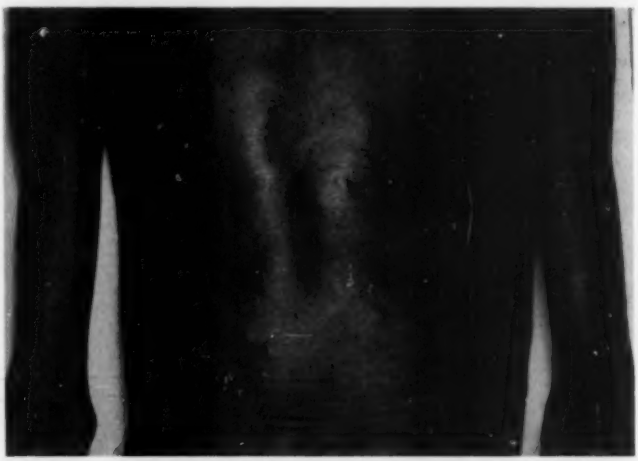

Fig. 3. Multiple cutaneous nodules are evident over the trunk.

is of the opinion that incomplete removal or surgical trauma may act to precipitate malignant degeneration in these tumors.

## DIAGNOSIS.

In a patient with generalized neurofibromatosis and symptoms of hoarseness, and/or dyspnea, and/or dysphagia, one strongly suspects the possibility of laryngeal involvement. On examination of the larynx, a smooth, submucosal mass is evident, usually in the area of the arytenoid and aryepiglottic fold. The extent of the lesion may be further evaluated by direct laryngoscopy and roentgenograms of the neck, including

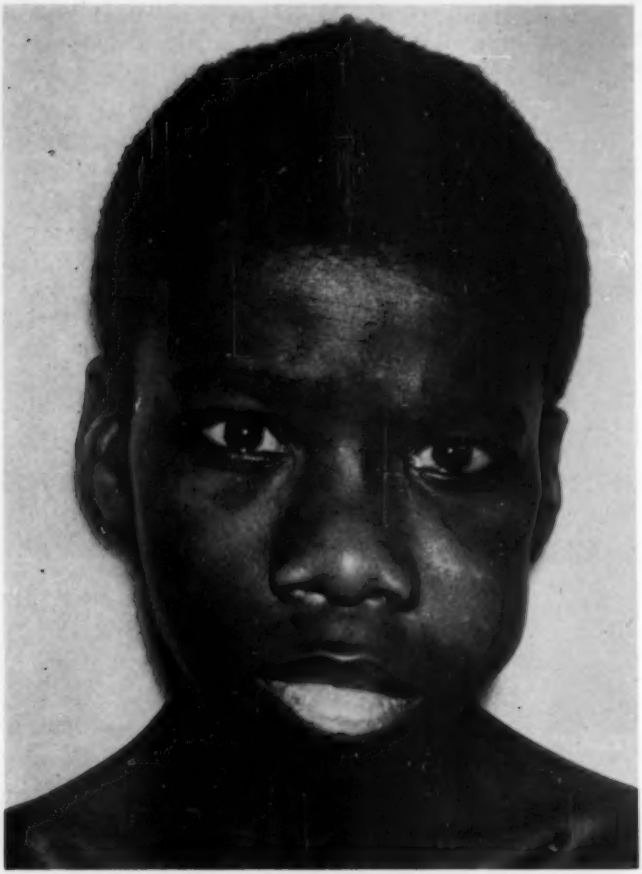

Fig. 4. Here the patient exhibits the cutaneous nodule over the left cheek.

laryngograms and laminograms. In cases where clinical findings are doubtful, a biopsy should be obtained for confirmation.

## REPORT OF A CASE.

J. G. is a 19-year-old Negro male, who was first seen in the Department

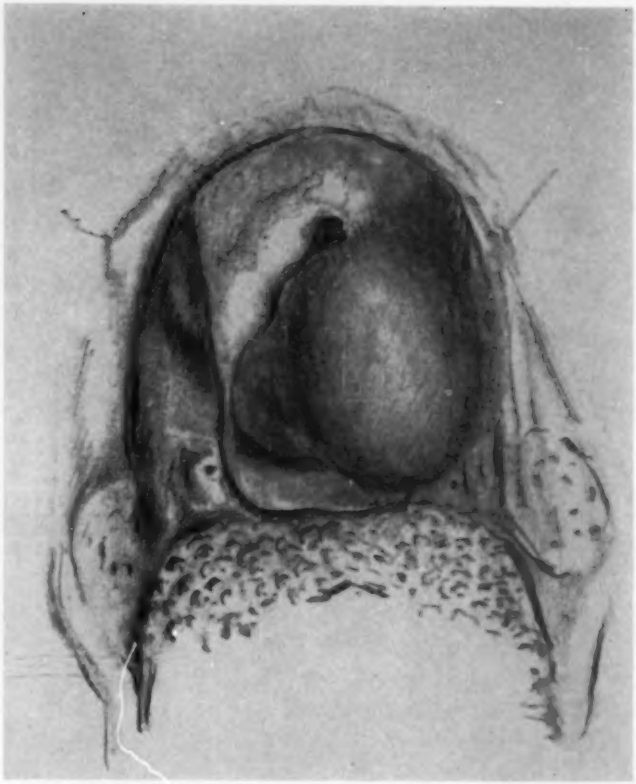

FIG. 5. An artist's sketch reveals the extent of the lesion in the larynx. Note the encroachment of the laryngeal lumen by the mass.

of Otolaryngology on Nov. 5, 1957, with a two-year history of progressive hoarseness and "noisy" breathing. Prior to that time, he had been followed in the Endocrine Department because of selective hypofunction of the pituitary gland and hypoadrenalism. A diagnosis of multiple neurofibromatosis was made in 1948 when biopsies from the left cheek and other cutaneous surfaces were taken.

*Past History:* He was found to be mentally and developmentally retarded, but nevertheless completed the ninth grade in school.

*Family History:* His maternal grandfather was four feet, ten inches in height, and had "many skin tumors." His mother has typical mollusk-like neurofibromata over the posterior neck area.

*Physical Examination:* General examination revealed a thin, short (four

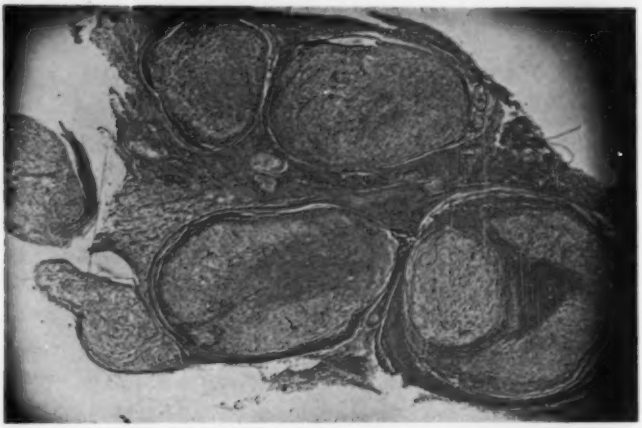

Fig. 6. Microscopic appearance of lesion under low power.

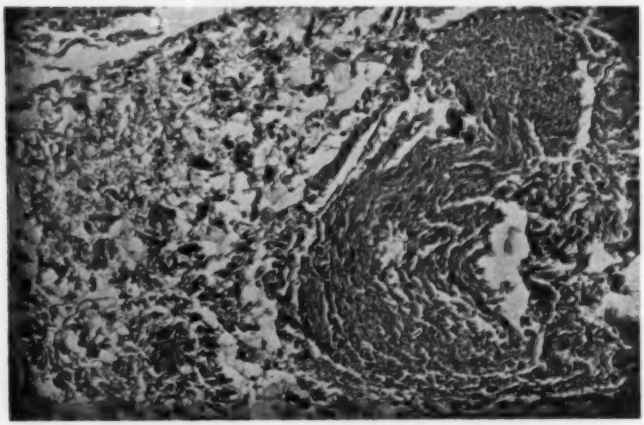

Fig. 7. Microscopic appearance of lesion under higher power.

feet, eight inches), colored male weighing 50 pounds (see Fig. 2). There was an obvious anterior chest deformity and scoliosis. Sensorium was clear but below chronological age. Over the trunk and extremities were multiple 1x2 cm. cutaneous nodules (see Fig. 3), with pigmented macules on his back measuring 1 to 5 cm. in diameter. There was also a 3x4 cm. mass involving the left cheek (see Fig. 4). He exhibited marked

hoarseness and inspiratory stridor. Indirect laryngoscopy revealed a large, submucosal mass involving the left arytenoid, left aryepiglottic fold with almost complete filling of the lumen of the larynx and obliteration of the pyriform fossa.

On Nov. 27, 1957, a preliminary tracheotomy was performed, after which, under general anesthesia, a horizontal skin incision and dissection through the thyrohyoid membrane exposed the tumor mass. It was directly continuous with the left superior laryngeal nerve and occupied the entire region of the left arytenoid, left aryepiglottic fold and left ventricular band (see Fig. 5). The tumor was poorly encapsulated and firm adherence to the mucosa necessitated entry into the pharynx at several points. A portion of the left arytenoid cartilage was also removed with the specimen. Mucosal surfaces were approximated to afford primary healing.

*Pathology:* Grossly, the specimen had a pearly white color, nodular surface and was pyramidal in shape, measuring 8x4x2 cm. Microscopically, there were hypertrophied masses of loose tissue with sheets of cells arranged in whorled-like fashion (see Figs. 6, 7). The smaller masses were similar to nerves.

*Diagnosis:* Plexiform neurofibroma.

## COMMENT.

The case presented gives a typical picture of multiple neurofibromatosis with generalized cutaneous nodules, "cafe-au-lait" spots, bony deformities and mental deficiency. The family history points to the hereditary tendency of this disease. In addition, there is the selective pituitary hypofunction with dwarfism and adrenal insufficiency. The small stature of the maternal grandfather is an interesting historical fact.

The presence of laryngeal involvement is a rare concomitant finding, but the location and gross observations herein described are in accord with those few cases reported in the past.

Surgical excision via a lateral pharyngotomy or thyrotomy approach appears to be the safest and surest means of complete removal of this type of tumor, especially in our case, where it was so poorly encapsulated.

## SUMMARY.

*1.* Multiple neurofibromatosis with associated laryngeal involvement is a rare finding.

*2.* A case is presented of multiple neurofibromatosis with

concomitant laryngeal neurofibroma, selective pituitary hypofunction and hypoadrenalism.

*3.* Pathologic factors, diagnosis and treatment are discussed.

ACKNOWLEDGEMENT.

Our sincere thanks and appreciation to Dr. James E. Croushore for his aid in the preparation of this paper.

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Box 250, R. R. 3.

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## SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

The Sixth International Congress on Diseases of the Chest will be held at the University of Vienna from August 29 to September 1, 1960.

# GLOMUS JUGULARE TUMORS.

## A Report of Seven Cases.*†

CHARLES E. KINNEY, M.D.,
and
OLIVER J. THOMS, M.D.,

Cleveland, O.

Glomus jugulare tumors are rather rare lesions arising from cells first identified and described by Stacy Guild in 1941,[1] situated in the adventitia of the jugular bulb and the ramus tympanicus of the glossopharyngeal nerve.

Following the first documented case of this tumor reported by Harry Rosenwasser in 1945,[2] the literature on this subject has progressively enlarged from the 18 cases reported by the Armed Forces Institute of Pathology in 1951,[3] to a single series of 23 patients documented in 1958.[4]

This article is to report a series of seven glomus jugulare tumors accumulated from 1947 to 1958 in the office practice of Dr. C. E. Kinney.

*Case 1.* This 43-year-old white female was first seen in 1945 with a chief complaint of left ear pain. All symptoms were referred to the introduction of a hairpin into the ear 15 years prior, following which fragments of tissue were intermittently removed from the ear for about one year. Four years later a biopsy was performed, and the patient received multiple X-ray treatments for three years. Two episodes of bleeding were recalled, in addition to a frequent ear discharge.

When examined, there was dry blood on the canal floor and a pink colored thickened drum which appeared to pulsate. No true granulations were present. Hearing was 50 per cent of normal in the left ear.

Frequent examinations for the next two-and-a-half years showed little subjective or objective change until pain developed, and the drum became redder and bulged. A radical mastoidectomy was performed in 1947 for a tumor mass filling the middle ear, mastoid cavity, and eroding the wall of the lateral sinus. Bleeding was severe and was controlled by cautery and packing.

The patient is 12 years postoperative and has no recurrence of the tumor. Microscopic diagnosis was granulation tissue until the second case alerted the observers to the glomus jugulare diagnosis.

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*Read before the Detroit Otolaryngological Society, March, 1959.

†From the Otolaryngological Service, Saint Luke's Hospital, Cleveland, O.

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*Case 2.* This 46-year-old female was seen in 1950, complaining of intermittent but increasing cricket sounds in the right ear of six months' duration, and a loss of hearing on that side.

The only abnormal finding on complete visual otolaryngological examination was a complete paralysis of the right vocal cord. Pure tone air conduction audiometry showed that she had 40 per cent hearing in the involved ear, and bone conduction testing showed that this loss was mainly of the perceptive type. Caloric vestibular tests on this side showed that there was hypo-activity of this labyrinth. Mastoid and occipital view X-rays of the skull showed nothing abnormal.

It was advised that she be hospitalized for further study but she chose to go to a large clinic in another state. Here a diagnosis of probable intramedullar lesion was made, and she was told that the operative mortality in such cases was over 90 per cent.

Two years later and with further hearing loss, headache, dizziness, nausea, and vomiting, the patient was admitted to our hospital. Neurological consultation was secured and a jugular foramen tumor diagnosed. A suboccipital craniotomy was performed, and a glomus jugulare tumor was removed from the right cerebellar pontine angle and jugular foramen. Postoperatively the course was satisfactory, except that one year later a redness of the lower aspect of the right drum developed which was typical of a glomus jugulare. The ear was treated by irradiation.

This patient is seven years postoperative and has residual neurological changes as well as evidence of tumor in the middle ear.

*Case 3.* This 60-year-old white female was seen in 1950 with a chief complaint of left earache and discharge. From about the age of 33 there had been a hearing loss on that side. A growth was found in the ear two years prior to the admission examination, and for the recent three weeks there was constant aching and discharge.

Auditory acuity was 35 per cent of normal. The ear canal was completely filled with a large granular and necrotic polyp surrounded by a mucopurulent discharge.

The patient was admitted to the hospital and following removal of the polyp, the diagnosis of an ulcerated, polypoid adenoma of the ceruminous glands of the ear canal was returned. Postoperative visits revealed persisting tumor in the floor of the anterior wall of the ear canal, although the drum was normal except for an anterior inferior perforation. Ten months later a recurrent tumor of similar diagnosis was removed.

Two years thereafter, there was a severe hemorrhage from a smooth polypoid tumor of the canal which clinically was diagnosed a glomus jugulare. A review of the previously biopsied material proved the diagnosis to be correct. In 1953 the patient was hospitalized, and a left open carotid arteriogram showed some filling of the tumor mass, following which the external carotid artery was doubly ligated. Four days thereafter a radical mastoidectomy was performed with moderate bleeding from the tumor extending posterior to the lateral sinus, to the digastric groove, the posterior canal wall, the paralabyrinthine cells, and filling the middle ear. Approximately 98 per cent of the tumor was removed and the ear packed. Tissue examination substantiated the clinical diagnosis. The ear was irradiated postoperatively but eight months later required further similar treatment because of tumor recurrence.

The patient is now living and without recurrent tumor after six years.

*Case 4.* The chief complaint of this 39-year-old white female was continuous buzzing and decreased hearing in the right ear for approxi-

Fig. 1. Radiogram showing destruction of the floor of the left posterior and lateral middle cranial fossa and base of the petrous portion of the temporal bone.

mately three months. Four days prior to the examination, the patient had a right myringotomy performed which resulted in considerable bleeding.

The hearing on the right was 89 per cent of normal. There was dry blood near the posterior aspect of the drum which was thickened and red. X-rays were normal of the mastoid bone. A biopsy, using the Rosen technique, diagnosed a glomus jugulare tumor. Four days later a right complete radical mastoidectomy was performed for the tumor in the hypotympanic space and extending to the Eustachian tube.

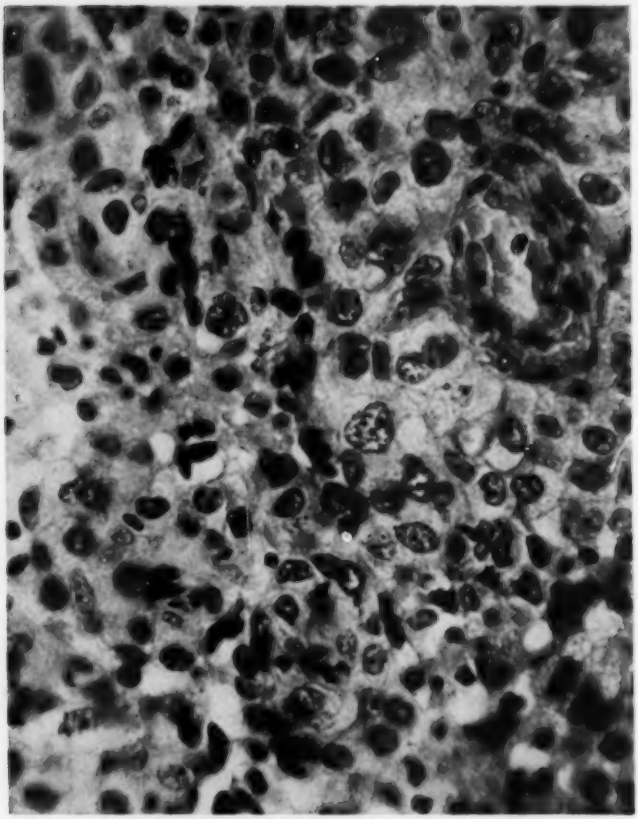

Fig. 2. Photomicrograph of malignant tumor composed of lobulated sheets of irregular cells containing frequent mitotic figures with no attempt at differentiation (H and E, X500).

The patient after four years is without evidence of recurrence.

*Case 5.* This 48-year-old white female complained of decreased hearing, fullness and pulsation in the left ear when first seen in 1955. Nine years prior, the patient was treated for tinnitus on the left and three years prior, a biopsy of a growth coming out of the drum was reported as granulation tissue.

The left audiogram disclosed the level to be 56 per cent of normal. Two red pusating masses were found protruding from the posterior junction of the drum and canal wall. Temporal bone X-rays were positive for areas of cellular destruction near the antral portion adjacent to the

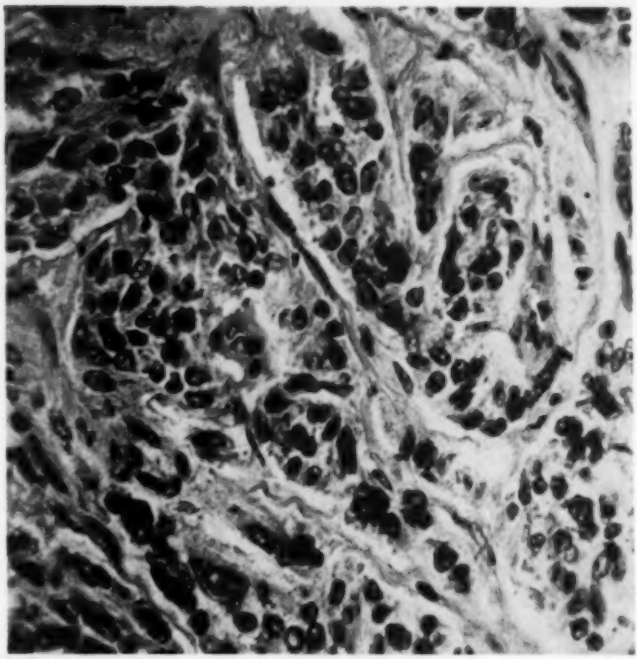

Fig. 3. Photomicrograph of tumor composed of nests of compactly arranged cells in acinar formation in a richly vascularized stroma (H and E, X500).

middle ear cavity. The patient was hospitalized and although a left open carotid arteriogram failed to delineate the tumor, the external carotid artery was doubly ligated. The following day a tympano-attico-apictomy was performed with little bleeding for a tumor in the mastoid cavity, middle ear, and Eustachian tube orifice. Pathology reported a glomus jugulare.

The patient is living without recurrence four years postoperative.

*Case 6.* Of considerable interest is this 58-year-old white female seen in 1957. Eighteen months prior to the first visit, a spontaneous left facial paralysis had developed, followed in ten months by considerable intermittent pain in and about the left ear. A hearing loss of two months was observed by the patient. One month before the visit, the patient had severe pulsating pain in the ear, and a left ear operation was performed in Europe.

The first examination disclosed marked swelling of the post-auricular incision and when cleared away, a red, granular, friable, bloody tissue was found. X-ray of the chest was normal, but the skull showed destruction of the floor of the left posterior and lateral middle cranial

fossae, as well as the base of the petrous portion of the temporal bone and mastoid process (see Fig. 1). A biopsy returned as undifferentiated malignant tumor cells of the ear canal.

A left post-auricular exploration of the mastoid area was performed, and a partial removal of the tumor mass accomplished. The entire mastoid cavity was filled with tumor which had eroded the tip and lateral sinus. The area was packed and closed. Microscopically the tumor consisted of lobulated sheets of cells approximating acinar formation. Numerous mitotic figures were present (see Fig. 2). The diagnosis was glomus jugulare tumor, malignant, of the left mastoid region. The tumor was a sharp comparison to the benign character usually seen (see Fig. 3). Irradiation therapy was begun, but the tumor continued to increase in size despite therapy.

The patient expired in 1958, 11 months after surgery, with symptoms suggesting rapid intracranial invasion. This occurred in northern Vermont and no autopsy was obtained.

*Case 7.* This 65-year-old white female presented herself with a pain and pressure in the right ear of two months' duration. Eight years previously, a sudden dizzy spell and hearing loss developed and she was informed that a blood vessel had broken in the right ear.

The right ear hearing was 20 per cent of normal. A partially bleeding, fibrotic tumor was found filling the entire canal to the external meatus. A severe hypertension was present.

Biopsy of the mass was reported as a granuloma pyogenicum and the following day the entire tumor was snared from the canal. This specimen was reported as a glomus jugulare tumor, and the patient was treated by irradiation rather than surgery, due to her poor physical condition.

Two years since treatment with over 5,000 *r* there is beginning regrowth of the tumor.

These seven female patients varied in age from 39 to 65 years, with an average age of 51 years. This corresponds well with the incidence of this tumor in the young and middle aged adults. A pulsating tinnitus and an early conductive hearing loss were the most frequent complaints. Other symptoms included otorrhea, bleeding from the ear, facial paresis, vertigo, inner ear deafness, and headache. Symptoms were present from three months to 17 years prior to the diagnosis of the tumor.

All cases except Case 2 presented a tumor mass in the auditory canal or behind the tympanic membrane. In these cases the Brown test proved of considerable value in the clinical diagnosis prior to biopsy. In one case, not here documented, the tumor failed to blanch on positive pressure with the Siegel otoscope, and no increase in pulsation or redness was noted with negative pressure. Subsequent biopsy diagnosed a squamous cell carcinoma.

Several cases presented the difficulties encountered in the microscopic diagnosis of this tumor. The first, removed early in the period of recognition of this entity, was diagnosed an endothelioma until the second case altered the observer's opinion. Another case biopsied was reported as a granuloma until the entire tumor was removed and examined, revealing a deep glomus jugulare tumor. In the two cases in which the external carotid artery was ligated, the bleeding was presumed to be reduced by the procedure.

These cases present the problems encountered in early diagnosis, as well as the importance of prompt and adequate treatment, careful follow-up and the recognition of the malignant potential of this tumor. When adequately studied, diagnosed, and treated, we believe the prognosis for these patients is good.

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## THE UNIVERSITY OF MICHIGAN MEDICAL CENTER.

The annual Otolaryngology Conference at The University of Michigan will be held April 21, 22, and 23, 1960, under the direction of Dr. James H. Maxwell, Chairman of the Department of Otolaryngology.

Applications may be addressed to the Department of Postgraduate Medicine, University Hospital, Ann Abor, Mich.

# HOW EFFECTIVELY CAN THE LARYNGECTOMEE EXPECT TO SPEAK?

## Norms for Effective Esophageal Speech.

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and

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The present sources of materials related to esophageal speech have little to offer in the way of direct information on how effectively the laryngectomee may reasonably expect to speak. The typical laryngectomee is concerned with such vital questions regarding his speech performance as the following:

*1.* How many words and syllables can be spoken per charge of swallowed air?

*2.* How long does it take to swallow a charge of air?

*3.* What rate in words per minute can be achieved relative to normal speakers?

*4.* What possibilities of pitch level and pitch variety can be anticipated for esophageal speakers?

The word *frequency* will hereafter be used in place of *pitch* because we measure frequency, which in turn is perceived as pitch. By way of example, we hear middle C and the octave below it as perceived pitches, but these are represented physically as 256 cycles per second and 128 cycles per second.

The laryngectomee would be benefited by some practical normative statistical information about the possibilities he could reasonably expect to achieve in successful esophageal speaking.

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It is the purpose of this report to describe generally the time and frequency performances of six superior esophageal speakers utilizing speech samples of adequate length for which norms for rate, breathing and frequency are already available for normal or superior speakers.

## SUBJECTS.

Superior esophageal speakers were selected so that any generalizations might serve as suitable and attainable goals for those learning to speak without a larynx. An initial group of 52 satisfactory performers from Southern California was obtained through contact with otolaryngologists, speech therapists, the Veterans Administration, The American Cancer Society, The Lost Chord Club of Los Angeles, and the New Voice Club of San Diego. The senior author screened this group successively to 23 and ten. Eight skilled and experienced judges selected six of the ten performances as best on a rating scale of general effectiveness. The Fairbanks "Rainbow Passage"[2] was recorded for each performer, "as though speaking to an audience of 25 people."

All of the selected speakers were males with at least four years of experience with esophageal speaking. Three of the speakers were experienced teachers of esophageal speech. There were excellent female speakers in the original group, but none appeared to match the performance of the male subjects who were finally selected. Six judges were requested to select female voices from the male voices on the basis of recordings alone. The complete lack of success on the part of the judges tends to indicate marked similarity in the voices of male and female esophageal speakers.

Each of the six speakers performed at the highest level of esophageal speech, as defined by Wepman, MacGahan, Rickard and Shelton[3]; in other words, they spoke with continuity and without consciousness of the act of swallowing and eruction. The speech was easily and naturally produced without apparent thought or effort.

## RESULTS.

The answers to our four basic questions can be presented

from the data obtained with the six selected speakers. Because of the brief nature of this report, the sensitive electro-pneumography, and phonophotographic techniques have not been described in detail.

*1.* How many words (or syllables) may the laryngectomee expect to speak on each charge of swallowed air? The answer to this question must be interpreted in the light of one feature of the particular experimental situation involved in this present study. The superior esophageal speakers in this study were held to a loudness level suitable for an audience of 25 people. A constant check of sound pressure levels indicated that the speakers did maintain this level. A lowered intensity might well have increased somewhat the number of syllables spoken. The experimental study indicated that without exception these superior speakers took small charges of air efficiently and unconsciously. It should be noted that the normal superior speakers while reading the same "Rainbow Passage," did not begin to produce the syllables per breath claimed by some esophageal speakers.

Our study indicates the mean words per air charge range from 2.8 to 6.3 for esophageal speakers; this should be compared with 12.5 mean words per breath for normal breathing superior speakers. The extreme range for one esophageal speaker was 15 words (22 syllables); contrast with this one exceptionally superior normal speaker who, under identical conditions, spoke 36 words (50 syllables). The normal speaker read aloud with an average of 12.54 words per breath. This speaker had a wide range of performance and tended to utilize breathing phrases of 7 and 14 words. On the other hand, the esophageal speaker averaged 4.98 words per air charge and had a much narrower range of performance.

The syllabic values found in this study are somewhat higher than those found by Stetson,[4] who stated a limitation of from three to four syllables. The lowest average value in the present study was 3.8 syllables and the highest 8.7 syllables per air charge. These values, even when highly efficient performances are considered, are much more conservative than some information given recent wide publicity.[5]

*2.* How long does it take to swallow a charge of air? Esophageal speech, despite frequent air charges, is relatively efficient and pleasant to hear. In order to understand how this can be true, we need to know that the skilled esophageal speakers gulped air in from .42 to .80 seconds, mean values considered. This is unbelievably rapid "breathing," as rapid in fact as most normal speakers breathe for speech. It should be pointed out that superior speakers usually breathe only at phrase limits. The esophageal speaker utilized his air charge for approximately one and one-half seconds, during which time he averaged 2.8 to 6.3 words, and so it is obvious that he needed air charges not only at phrase limits, but also many times in between. This is contrasted with the normal speakers who utilized their breath for 4.19 seconds and spoke 12.5 words. If relative time or words per air charge is taken as a measure of efficiency, the normal speaker was from 2½ to 3 times more efficient than the esophageal speaker.

*3.* What rate in words per minute can be achieved relative to normal speakers? It is probably most reasonable to combine the factors of Questions *1* and *2*, and to use total words per minute as a measure of efficiency. When this was done, the average for the superior esophageal speakers was 113 words per minute, compared with a rate of 166 words per minute[1] for the average normal speaker for the same reading material. Considering this measure, the normal speaker spoke only 1.47 times the rate of the esophageal speaker. Stated another way, the esophageal speaker was 80 per cent as rapid as the average normal speaker. Although the esophageal speaker would be judged as "too slow" compared to normal speakers, this is of little consequence if his efficiency is relatively satisfactory. The superior esophageal speakers did perform efficiently with the 300-word speech samples in the present study.

Preliminary study indicated that the skilled esophageal speakers could not speed up their rate without sacrificing either loudness or suitable phrasing. Even with the superior speaker the ability to modify rate is severely limited by the need for frequent air charges.

*4.* What possibilities of frequency level and frequency vari-

ability can be anticipated for esophageal speakers? The results of the experimental frequency analysis indicated that the superior esophageal group (for both the mean and median frequency) was essentially one whole octave lower than the comparative group of superior normal speakers. This, in fact, represents a very low pitch and may be identified to the ear by striking the second C below middle C on the piano; however, despite the difference in frequency level the distribution of frequency usage showed greater variability for the esophageal speakers than for the normal speakers. The standard deviation values were 7.0 and 4.3 tones per second. Four of the esophageal speakers used the highest frequency which was lower than the median frequency used by the lowest of the superior normal group. The total range of frequencies was 13.2 tones for the superior esophageal speakers compared with 10.5 tones for the superior normal group.

This striking and unexpected finding clearly negates any assumption that the esophageal speaker must be monotonous in pitch. In fact, it supports the contention that esophageal speakers can learn to sing simple tunes at a slow pace. The wide range of the values in this study possibly could be attributed to a much longer reading selection and some improvement in the experimental equipment. It should also be pointed out that these frequency variations are taking place at a very low level in the frequency range.

## CONCLUSIONS.

The authors feel that this study exploring the rate and frequency characteristics of superior esophageal speech may be useful in establishing realistic norms for those who must learn to speak in this unique way. This study has utilized much longer samples of speech than previous studies, and it is, therefore, believed that the results are highly reliable for these carefully selected superior speakers. All in all, the results are rather conservative, being much more optimistic for reasonably effective speech than earlier studies based on small samples, but far less optimistic than predictions for success in recent popular literature.

*1.* The esophageal speakers spoke relatively easily and were

no more conscious of the "breathing" function than were normal speakers.

*2.* The speakers of this study averaged 5 words (4.98) per air charge and performances averaged about 120 words per minute. A top limit of 11 to 12 syllables was very satisfactory; however, one speaker did achieve an extreme range of 22 syllables.

*3.* The air charge was gulped in about one-half second, a more rapid performance than that of some normal speakers inhaling for an intra-phrasal breath pause.

*4.* The mean frequency (pitch) level is almost exactly one full octave below that of the normal male speaker.

*5.* Contrary to some reports, frequency (pitch) variability is quite comparable to that of normal speech.

*6.* It is, however, very doubtful that the average frequency level can be raised much, if any, above 66-70 cycles per second.

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## THIRTY-THIRD ANNUAL SPRING CONGRESS OF GILL MEMORIAL EYE, EAR AND THROAT HOSPITAL.

The Gill Memorial Eye, Ear and Throat Hospital announces to the profession its Thirty-third Annual Spring Congress in Ophthalmology and Otolaryngology, April 4 through April 9, 1960. A formidable list of speakers will participate.

For further information write: Superintendent, P. O. Box 1789, Roanoke, Va.

# THE IMPORTANCE OF NASAL FRACTURES.*

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Boston, Mass.

The importance of nasal fractures lies in the fact that they are usually thought of as an insignificant type of fracture, and as such management is commonly on a "hit or miss" basis; yet, when one realizes that any imperfection in realignment of the nose can be very noticeable cosmetically, then it is understandable why a little more thought should be put into this subject.

If the history of a patient who presents himself for rhinoplasty is gone into, it is my impression, based on 50 such patients, that fully one-third of them will give a history of previous traumatic injury to the nose. If patients could remember all the traumatic events in their lives, especially in early childhood, probably at least one-half of these patients would give such a history.

## PRESENT DAY MANAGEMENT OF FRACTURED NASAL BONES.

At the present time the treatment of nasal fracture is not stressed very much in residency training programs. The usual routine consists of taking X-rays, inserting an elevator into one nares and elevating the nasal bones into a supposedly correct position. Asch forceps are also being used. Splinting, consisting of adhesive tape or Wood's metal over dental compound, usually is next applied. As will be mentioned later, there is a very small percentage of nasal fractures that should be reduced openly for better results.

## METHODS OF MAKING AN EARLY DIAGNOSIS.

One of our first problems is to make an early and correct diagnosis before attempting treatment. If the patient is seen early before edema has developed, inspection of the outside

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of the nose is very important. Sometimes a diagnosis is obvious, the nose is externally deviated or depressed. One very important point to remember, however, is that edema, especially in children, sets in very early and may fill in any deformity. This edema will result in the nose's being smoothly swollen when, in fact, it may be depressed; thus, a false picture may be obtained. In adults this edema forms later and may be less marked.

The bridge of the nose and bony vaults are next palpated for crepitus. One must not make the all too frequent mistake of palpating too vigorously, and causing further damage to the already splintered bones. One must also bear in mind that crepitus is not too common in fractured noses, as the fragments quickly become well splinted due to the early edema formation; therefore, a fracture may be present even though there is no palpable crepitation.

After the outside of the nose is examined, the inside is anesthetized and shrunken with 4 per cent cocaine packs. If the mucous membrane will not shrink down, one must ascertain whether the swelling is from the medial or lateral nasal wall. If from the medial wall, deviation of the septum and/or submucosal hemorrhage with hematoma must be considered. It must be emphasized that a hematoma of the septum has normal mucosal coloring and is not ecchymotic. Lateral swelling may be from buckling of the lateral cartilages and/or subchondral hemorrhage.

If the mucous membrane does shrink well, tears in the mucous membrane are looked for to show the site of the fracture or displacement of the septum, lateral cartilage or bony walls.

Finally, X-ray studies are done. I strongly believe that entirely too much emphasis is placed on an X-ray report of "no fracture seen." Too often a patient will be told that he does not have a fractured nose because an X-ray did not reveal it, and several years later he will have to have a rhinoplasty or submucous resection, due to resultant deformity. Reports in the literature[1,3] state that on the average only 50 per cent of nasal fractures are seen by X-ray.

At the Massachusetts Eye and Ear Infirmary we are fortunate, indeed, to have a radiologist having 36 years of experience in eye, ear, nose and throat X-ray. During this time he has developed a technique that I am sure gives much better than average results. His technique consists of three films: *1.* lateral view with good soft tissue contrast to show either depression of the dorsum of the nose, nasal process of the frontal bone, plus any displacement of the bony arch from before backwards; *2.* an exaggerated Water's view to show lateral displacement of the bony arch; *3.* his own special view consisting of a dental film inside the mouth with the X-ray beam tilting down from the top of the head in such a way as to miss both the frontal bone and the teeth, but to include the bony nasal arch, and thus pick up the displacement. He feels that with this technique most bony fractures are seen.[10]

## CLASSIFICATION OF NASAL FRACTURES.

For the purpose of analysis, the 100 cases of nasal fractures studied by the author at the Massachusetts Eye and Ear Infirmary have been classified into simple and comminuted, with subdivisions modified after Becker.[1]

A green stick fracture was one in which there was a bending of the nasal bones and septum, but no actual true fracture.

A linear fracture without displacement was a simple fracture that was in good position and could be treated successfully with little skill and care. Treatment in all cases consisted of ice and pain medication. If either lateral displacement or depression was present, treatment consisted of blunt elevation, with or without splinting and/or intranasal vaseline gauze packing.

A comminuted open fracture was one in which the nasal bone was shattered into multiple pieces and there was a mucosal tear exposing bone. Treatment was the same as for depressed or displaced lateral fractures.

Using the above classification, the 100 cases could be broken down as follows:

*A. Simple Fractures—*

1. Green stick—14 patients.
2. Linear without displacement—21 patients.
3. Linear with either lateral displacement or depression—37 patients.

*B. Comminuted Open Fractures*—28 patients.

The ages of the patients ranged from 3 years to 74 years; however, if we divided nasal fractures into adults and children, using age 16 as a dividing line, we find that 39 of the 100 patients were children. Children had 12 of the greenstick fractures, one of the linear fractures without displacement, 16 of the 37 displaced or depressed fractures, and 11 of the 28 comminuted open fractures.

The most common type of nasal fracture in adults is the one with lateral displacement or depression.

## RESULTS OF TREATMENT.

To evaluate the results of treatment, the author compared the pre-treatment X-rays and photographs of patients with the post-treatment X-rays and personal clinical examination. A result was considered good if the author could find no post-treatment clinical or X-ray evidence of external or internal nasal deformity. A result was considered improved if the position of the displaced or depressed bone or cartilage on post-treatment X-rays had changed from that recorded on pre-treatment X-rays, but deformity was still present on clinical examination. In other words, an improved result may still have a resulting deformity, only this deformity is less than would have been if not treated. A result was considered poor if the alignment of the fractured bone or septum had not changed in position when the pre- and post-treatment X-rays were compared, and also pre-accident photogrophs were compared with the present clinical condition.

The results of the treatment were as follows:

*A.* 14 Greenstick fractures—100 per cent good results.

*B.* 21 Linear fractures without displacement—100 per cent good results.

*C.* 37 Linear fractures with:

*1.* Displacement—40 per cent good results, 35 per cent improved results, 25 per cent poor results.

*2.* Depression—20 per cent good results, 25 per cent improved results,, 45 per cent poor results.

*D.* 28 Comminuted open fractures—10 per cent good results, 20 per cent improved results, 70 per cent poor results.

## ANALYSIS OF 100 CASES.

During the two years preceding December 31, 1957, there were 162 cases of nasal fractures treated by residents of the Massachusetts Eye and Ear Infirmary. The author personally examined 100 of these patients at least two months' post-reduction, and he did the initial fracture reduction in 21 cases. The 79 remaining cases were treated by seven other residents. The time between the accident and the initial treatment varied from one hour to 52 hours. In the majority of patients, the treatment consisted of elevating the depressed nasal bones with a blunt elevator and replacing the displacement by digital pressure toward the midline. Asch reduction forceps were available only during the last three months of the study (16 cases) and external and internal splinting was used on only 20 cases.

It is interesting to note that a few of the patients were told that their fracture was "reduced the best that could be done without doing plastic surgery."

For the purpose of analysis, the 62 cases on which we have no follow-up, will be disregarded.

We have no way of evaluating how the nose looked when the doctors finished reducing the fracture, but, after all, the patient is not interested in this point, only the final result. Accordingly, this study evaluated only results from two to 18 months after reduction.

## POSSIBLE FACTORS CONTRIBUTING TO POOR RESULTS.

It is my own personal feeling based on the 21 cases in which I did the initial treatment, that one of the most important factors contributing to poor results is that posttramatic swelling, by filling in the depressions, may obscure a deformity that has not been corrected; also, while the nose may be reduced to the correct position, if it is not held in this position by splinting there is a tendency for it to slip back or fall down again. Forman's[7] comparison of the architecture of the nasal pyramid to an arch is a very good one, for when the lateral buttresses and abutmens are broken, the keystone and side walls of the arch will collapse. The same thing will happen with a fractured nose. The nasal bones and frontal process may be reduced to perfect position, but if there is no provision made to give support artificially either directly in the form of an uplift, as with intranasal packing or indirectly in the form of lateral support to the buttresses or ascending processes in the form of external nasal splinting, or both, then the nasal pyramid may collapse or be in imperfect position.

The results at the Massachusetts Eye and Ear Infirmary bear out this fact. In the type of fracture where support by splinting is needed and was not given, we have very poor results. In those cases where we did not need splinting, we obtained very good results.

Another factor contributing to some of the poor results was the fact that Asch or Walsham forceps were not available during this two year period for those cases in which there was locking of displaced fragments. If one uses merely a blunt elevator, it is very difficult at times to replace perfectly the septum into the groove of the vomer, to unlock a displaced and depressed ascending process, or to correct overriding nasal bones upon the maxilla.

A third reason for our own poor results, in the author's opinion, is that no attention has been paid to damage to the upper and lower lateral cartilages, the osseous vault and sometimes the septum receiving all the attention. It should be emphasized that, if a hematoma forms around these cartil-

ages and is not corrected, it will lead to curling and fibrosis with resulting deformity.

### SUGGESTED METHOD OF TREATMENT.

There is nothing new that can be added to the treatment of fractured nasal bones that has not been written in the literature many times by many authors.[1,2,3,4,5] The prime requisite, however, is a working knowledge of the anatomy and relationships of the bony arch and cartilaginous structures, including the septum.

Several points in the anatomy of the bony arch are important enough to be mentioned here. First of all, the nasal part of the frontal bone extends downward behind and beneath the nasal bones and thus adds strength and support to the bony arch. It follows that a fracture which involves the nasal portion of the frontal bone will require more uplift and support to prevent postreduction depression of the bridge than a fracture that does not. While this type of fracture initially may be reduced quite easily, only with proper packing and splinting will postreduction depression be prevented.

Second, the lateral cartilages extend upwards on the inner surface of the nasal bones and are intimately fused with them; the clinical significance of this being that the lateral cartilages participate in displacement of the nasal bones and are rarely detached from them during trauma; thus, any damage to them, such as lacerations or hematomas, must also be corrected by suturing, evacuation, etc.

One must keep in mind also, that while the nasal bones heal by bony union without scar contraction, the nasal cartilages do not. They heal by an ingrowth of connective tissue and not by cartilaginous union. Cartilage may also curl and buckle from organization of inflammatory exudate, or chrondritis may set in and undergo calcareous degeneration with resulting cosmetic deformity.

After going through the previously outlined diagnostic steps, early evacuation of effusions and hematomas must be carried out to prevent cartilaginous damage. All locked fragments should be unlocked before any elevation takes place.

Using Asch forceps, the maxillary bones may have to be rotated outwards, after which the nasal bones or the naso-frontal process may be elevated easily. Lateral displacement can next be corrected by inward pressure by Asch forceps on the maxillary bones at the base of the nose. These procedures may or may not also correct the septum. If not, one may either have to replace it in the groove of the vomer by Asch forceps; or, under direct vision, push the upper fragments into position, using a septal elevator through a mucosal tear. After the bony and cartilaginous deformities are realigned, the nose should be packed internally along both sides of the septum either with half-inch vaseline gauze strips or half-inch gauze strips soaked with cod liver oil. The cod liver oil reduces odor and also makes removal much easier by preventing adhesiveness to the nasal mucosa such as vaseline gauze tends to produce. External splinting to prevent "widening" of the nose due to spreading of the ascending processes is next applied, using dental compound over the dorsum and also over the bony arch. It is important not to get the compound too pliable by using water that is too hot and also to have the compound "set" quickly by applying ice cubes directly on the compound. While "setting," constant digital pressure inward must be applied bilaterally in order that the compound will not relax and thus lose its splinting effect. If we do not splint the fractured nasal arch, it may tend to revert to its displaced position; therefore, the corrected position should be maintained by internal packing for five to seven days, and by external splinting for about ten days.

This brings us now to the very important subject of when to do an open reduction. It is my own personal feeling that one should be as conservative as it is practically possible. Naturally, all simple bony fractures can be treated by closed reduction, providing accurate diagnosis by inspection and X-ray is done beforehand. If there are any tears in the mucosa, a small probe should be inserted and palpation should be carried out in order to ascertain whether there is any exposed bone. If bone is palpated, then the original mucosal tear should be enlarged with a blade to obtain a good exposure, so that a precise reduction under direct vision can be accomplished. Hematomas or effusions of the cartilaginous

structures (septum or upper and lower lateral cartilages) must be evacuated by incision rather than needle aspiration, which will fail most of the time because partially clotted blood may be present that could block the aspirating needle. Open reduction should be used if old associated fractures are present, or if any other previous defect, such as a hump that the patient may want corrected, is present.

## NASAL INJURIES IN CHILDREN.

Children present a special problem as far as nasal injuries are concerned, because the anatomy of both the osseous and cartilaginous structures of the nose is different. There is less ossification and calcification of the nasal, vomer, and ethmoid bones which usually results in a bending or green-stick fracture rather than a complete through-and-through break; therefore, the valuable sign of crepitation may not be present. It follows, also, that less force is needed to produce the fracture in children. The cartilaginous structures of the nose not only are softer and curl easier, but they seem to form more scar tissue leading to a deformity that increases as the child grows.

When a child presents himself with a nasal injury, early reduction is very important because edema sets in very quickly and may obscure the picture by filling in the defects. The nose then may have a falsely smooth appearance. If edema is already present when the child first presents himself, it is very hard to determine the exact status of the injury without first decreasing the swelling. I believe that it is a mistake to tell the parents to apply ice for three or four days while we wait for the swelling to go down. Instead, inject the swollen tissue, using a 25 gauge needle, with 1 to 2 cc. of hyaluronidase to reduce swelling. After injection of the swollen tissue, the inside of the nose is sprayed with 1 per cent ephedrine sulfate, repeated three times, and then packed with long fiber cotton strips that have been dipped in the same solution and then wrung out. After a wait of five minutes, the packs are removed, and inspection of the inside of the nose is carried out, looking for tears in the mucosa, open fractures, or dislocation of cartilaginous structures.

X-rays are used only to confirm the clinical diagnosis and as a permanent record of the case.

Relatively uncomplicated fractures in children may be reduced in the emergency ward, and hospitalization is not necessary. A short general anesthesia rather than local is preferred for children. A thin layer of cotton moistened in 4 per cent cocaine and vaseline and wrapped around a periostial elevator is introduced into the nares beneath the depressed bone, and the nasal arch is elevated. The displaced bone is then replaced to its original position by digital pressure. I have found that it is necessary to maintain the corrected position by means of lateral splints as with adults, otherwise the bones tend to revert to their previously displaced position.

## SUMMARY.

In 100 cases of nasal fractures seen at the Massachusetts Eye and Ear Infirmary, the post reduction cosmetic results were not so good when the fracture was of the comminuted open type as they were with greenstick, or linear fractures with or without displacement or depression. The reason for this poor result is thought to be due to poor post-reduction splinting and packing. The literature is reviewed partially and a composite method for diagnosis and treatment presented.

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# ANTERIOR-POSTERIOR TECHNIQUE FOR THE TREATMENT OF CHRONIC OTITIS MEDIA AND MASTOIDITIS.

## Preliminary Report.*

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and
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The surgical treatment of chronic mastoiditis with cholesteatoma has been a great problem since the earliest days of otology. Ever since the first operations were described, radical mastoid surgery has remained relatively unchanged. In the postoperative period, our problems of healing begin. The newly created radical mastoid cavity tends to fill with granulation tissue requiring constant curettage in an effort to keep this exuberant granulation tissue under control. The granulation tissue often becomes infected. Many methods have been tried to clear or control the granulation tissue in an attempt to promote healing. These include X-ray therapy, the use of caustic solutions of silver nitrate and trichloracetic acid, curettage, and excision. Eventually, a fibroma may form, which completely fills and occludes the mastoid cavity. Atresia of the external auditory canal may accompany the filling of the mastoid cavity. Secondary operations to excise the fibrous tissue often become necessary, and secondary skin grafting may be needed. Numerous methods to control the size of the mastoid bowl and to hasten its healing have been suggested, including the use of fat grafts, cartilage grafts, bone grafts from the tibia, cancellous bone from the illium, muscle flaps, and plastic material of various sorts. These agents were all tried in an attempt to control the size of the mastoid cavity. During the 1930's an extensive bibliography was built up on methods of obliterating the mastoid cavity. This contains articles too numerous to record.

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In patients in whom the mastoid cavity heals, problems exist because of the presence of the mastoid bowl. Infections of the lining of the cavity may result. The patient should not get water in the mastoid cavity, since infection can occur from this. This elminates swimming. In children, especially, the care of a modified radical or radical mastoidectomy is a chore. A child will not tolerate too much in the way of post-operative care. Once the child has been subjected to a session of curettage, with its attendant pain and bleeding, he will rarely cooperate in further treatment.

It, therefore, occurred to us that since the cavity tends to close, and since we have been trying to devise various techniques to make the cavity small or to obliterate the cavity, why should we tolerate the radical mastoid bowl at all? It is recommended, therefore, that rather than do an endaural or postauricular radical mastoidectomy, which leaves a wide open mastoid cavity exposed to the outer world, we should carry out a procedure which we call the anterior-posterior technique. The posterior part refers to a classical postauricular mastoidectomy and the anterior to the exploration of the middle ear with an ear speculum and the operating microscope. In this way, there would be no mastoid cavity to care for, and one would not worry about the problem of granulation tissue and atresia. A number of patients have been operated upon in this manner with very good results. It is for this reason, that we present the preliminary report on this technique. No special claim is made for originality, except that we have combined techniques well known to us, in one operation, and thus avoid some of the distressing problems that occur in the classical endaural mastoid operations.

The operation is performed under endotrachial general anesthesia. The mastoid portion can be done first, or the middle ear portion first and the mastoidectomy last. The patient is prepared in the usual manner. The hair from the postauricular area is shaved for a small distance. The usual post-auricular incision is made and the mastoid cortex exposed. This procedure can be carried out, using the light from the draped Zeiss microscope for illumination and magnification and for completing the various steps of the operation. The

mastoidectomy is carried out with cutting burs and curettes. When the mastoidectomy has been completed, the additus is widened and the epitympanic space exposed. The incus and malleus are then skeletonized and cleansed of all diseased membrane. Any cholesteatoma, granulation, and scar tissue is removed from the ossicles, the epitympanum, and some of the tympanic cavity below the incus. When this portion of the operation is completed, the posterior canal wall is thinned but not removed. A bridge of bone is allowed to remain over the auditory ossicles to protect the incus and malleus. If the ossicles are diseased or partially necrotic, the incus and head of the malleus may be removed. This portion of the operation is done under 16X magnification. By this approach, the upper portion of the epitympanic recess well into the middle ear, can be explored. A small No. 190 plastic tube (see Fig. 1) is put into the attic region and sutured to the upper angle of the wound. A No. 8 rubber catheter is placed in the lower portion of the wound and sutured to the lower end of the wound. A small piece of tape is placed around the upper catheter so that it cannot slip into the mastoid cavity. The post-auricular wound is then closed with interrupted silk sutures in the classical manner.

The operation is then switched to the middle ear, and is done under 10X to 16X magnification. The canal walls are injected, and through the ear speculum a Shea triangular incision is made. This incision can be extended anteriorly, both superiorly and inferiorly to expose the entire hypotympanum. The middle ear is then inspected. Cholesteatoma matrix and granulation tissue is removed as well as the ossicles, should they be diseased. Practically all of the middle ear can be visualized in this manner. The stapes is exposed and freed of scar tissue and granulation tissue. If the ossicular chain is intact, the drum is allowed to fall back in the usual manner. If the ossicles have been removed, a small piece of No. 90 plastic tubing is fitted as a couplet over the head of the stapes. The posterior superior area of the middle ear cavity is also carefully cleansed, and all of the diseased tissue is removed far posteriorly and superiorly until we meet the place where the debridement was stopped on the mastoid side of the operation; thus, the entire attic and middle ear

Fig. 1. First postoperative dressing. Note presence of plastic tube in upper angle of wound. This allows a projection of the tube out of the dressing, so that the nurses or residents can introduce appropriate antibiotic solution.

can be cleansed of infection, granulation tissue, and cholesteatoma. The tympanic perforation is handled by cleansing the edge of the perforation and removing the infected granulation tissue. Any remaining polypi or granulation tissue can be removed with a small punch and curette. Usually, there is a

fair amount of bleeding, when the incision is first made and the middle ear entered, but as the diseased membrane is removed, the bleeding stops. This can be controlled by small gelfoam sponges soaked in epinephrine 1:1000 solution or in thrombin topical solution. After this portion of the operation is completed, the drum and skin flap are eased back into place and held with small pieces of gelfoam packing.

In the postoperative period, Neomycin or other appropriate antibiotic solution is introduced into the plastic tube in the upper angle of the wound. This tube is allowed to project from the dressing. The solution is put in three to four times daily while the patient is hospitalized. The tube is allowed to remain in place for many weeks, if necessary, and can be covered with a small dressing. The drainage tube, which is in the lower angle of the wound, is removed on the fifth to seventh day. The tube in the upper angle of the wound is allowed to remain until the ear becomes dry, since this can be used to introduce antibiotic solution or to irrigate the middle ear. The tube can be seen in the attic region when the drum is inspected through a speculum. As the ear clears up, the perforation in the drum can be seen to close with a layer of scar tissue.

This operation has been done on patients with cholesteatoma and attic perforations. The perforation is not closed, but when the middle ear becomes dry, it usually seals and heals itself with the formation of scar tissue. When the perforation heals, if there is an intact ossicular chain, the hearing is usually at a high level. If the ossicles have been removed and a plastic tube is placed on the stapes, a myringostapedopexy is produced and a good hearing level results. This same operation can be carried out when a larger perforation is present or even when more of the middle ear has been destroyed. The operation can be completed by use of a skin graft or myringoplasty over the promontory, or a myringoplasty-tympanoplasty can be done at a later date when the ear is dry.

In our patients, healing was very rapid and occurred in from two to four weeks. The number of postoperative visits

and manipulative procedures is cut to a minimum, which is pleasing to both patient and otologist.

SUMMARY.

A preliminary report of a surgical technique is presented. We have called this the Anterior-Posterior Technique. This includes performing a post-auricular complete mastoidectomy to eliminate the mastoid disease and an operation through an ear speculum and the operating microscope to eliminate middle ear pathology. This technique offers rapid healing with a dry ear, without the disability of an open mastoid cavity, granulation tissue, drainage, and long protracted healing. There is minimal postoperative care. The mastoid cavity wants to heal and close; therefore, we let nature take over. The middle ear can be handled by the approach through the ear speculum and with the use of the operating microscope. This makes for rapid healing and is known to all otologists. Variations of this technique can be applied to include myringoplasty and tympanoplasty, with grafting and plastic prosthesis. A dry ear with an improvement in hearing results.

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# GUSTATORY SWEATING AND FLUSHING.*

## The Auriculo-Temporal Syndrome—Frey's Syndrome.

WILLIAM GARTH HEMENWAY,

Chicago, Ill.

That sweating and flushing of the cheek may occur after parotid surgery, injury, or infection has been recognized for many years. As the phenomenon has not been reported in recent American literature it appears that many physicians are unaware of the condition. Patients presenting these symptoms may be misdiagnosed, subjected to needless investigation and consultation, and labelled as psychoneurotic. As the frequency of parotid operations has increased during the last decade more cases are being seen.

A few weeks or months after an injury, operation or infection in the region of the parotid gland, the patient may notice that an area on the side of his face anterior to the ear begins to flush and sweat when he eats. Certain foods, such as lemon and apples are more prone to elicit the symptoms than others. Either sweating or flushing may come on first, and occasionally one may be present without the other. Symptoms vary considerably in severity, and the condition persists indefinitely.

This paper will review some of the literature, present two recent cases and suggest a possible satisfactory treatment.

Duphenix[1] is credited with reporting the first case in 1757. Symptoms developed following drainage of a parotid abscess. In 1853 Baillarger[2] reported a bilateral case after parotid infection. Weber[3] described a case following suppuration of the parotid lymph nodes. Lucie Frey,[4] of Poland, reported a case in 1923. The patient had sustained a bullet wound in the parotid area and later developed typhus and typhoid fever. She was the first to observe that the sweating and flushing

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occurred over the distribution of the auriculo-temporal nerve. The condition has often been called Frey's syndrome or the auriculo-temporal syndrome. In 1932, two patients with this syndrome were reported by Peter Bassoe[5] of Chicago. One patient had a mixed tumor removed, and the other followed drainage of surgical parotitis.

In 1948 Freedberg, et al.,[6] collected only 35 cases from the literature; however, due to the great increase in the number of parotid operations being done, many more cases have been reported in the past few years.

Recently, interest in the subject has been renewed by Laage-Hellman of Gothenberg, Sweden, and by Glaister, et al., of Middlesex Hospital, London.

Laage-Hellman[7] investigated 123 patients who had undergone conservative parotidectomy. He employed the Minor Starch-Iodine test to study sweating. The face and upper neck are painted with a solution of iodine, castor oil and alcohol, and starch powder is sprayed thinly over the area. The patient sucks on a lemon slice. Each functioning sweat gland is seen as a blue spot which may coalesce (see Figs. 1 and 2). In response to a direct inquiry, 76 of the 132 (62 per cent) patients replied that they had symptoms on eating. Twenty-seven reported both sweating and flushing, 32 had sweating only, and 17 had only flushing; however, when he examined the patients and used the starch iodine test, he could demonstrate gustatory sweating in all 123 cases. Ten showed sweating alone, and three showed flushing alone. The sweating was most frequently found over the distribution of both the auriculo-temporal and the great auricular nerves. Sometimes only the auriculo-temporal was involved and rarely only the great auricular. In only 16 cases (13 per cent) were symptoms severe enough to embarrass the patient. He concludes that the condition is an invariable sequel of surgery about the parotid, and that only occasionally are symptoms severe enough to disturb the patient sufficiently to require therapy. He prefers to call the syndrome Gustatory Sweating and Flushing (G.S.F.).

In 1958 Laage-Hellman[8] found an interval of five weeks to

Fig. 1. Case 1. Sweating over the distribution of the auriculo-temporal and great auricular nerves when the patient is chewing a lemon. The skin has been painted with iodine solution and sprayed with starch.

one year between surgery and the onset of symptoms in 58 cases. He points out that this latent period strongly favors the theory of misdirected parasympathic nerve regeneration as an explanation for the sweating and flushing.

Treatment is discussed by Laage-Hellman[9] in another recent publication. Cutting the auriculo-temporal would abolish the condition, but this is difficult to perform in an operated field and may be followed by regeneration and recurrence. The otic ganglion is inaccessible to surgery. Injection with alcohol would result in mandibular nerve anesthesia for several

Fig. 2. Case 2. Sweating over the distribution of the auriculo-temporal nerve. This was abolished by injecting the otic ganglion with local anesthesia.

months, which would probably be more uncomfortable than G.S.F. Intracranial division of the glossopharyngeal nerve has been effective but is too extensive a procedure for such a benign condition. X-ray therapy is effective in dosages sufficient to destroy the sweat glands. This takes about 5000 *r* which seems too much X-ray to use on a benign process. Systemic anticholinergic drugs have not proven practical, due to severe systemic effects. He recommends 3 per cent Scopo-

lamine Hydrobromide cream applied locally to the involved area every few days. This satisfactorily controls symptoms in most patients.

Glaister, Hearnshaw, Heffron Pick and Patey[10] state that sweating is the important feature which may or may not be accompanied by flushing. Two patients with the syndrome were very thoroughly investigated. Sweating was observed and recorded by a method described by Thomson and Sugarman.[11] Anesthesia of the mouth reduced but did not abolish the sweating. Local injection of atropine prevented the sweating from appearing. Blocking the auriculo-temporal nerve with a local anesthetic stopped the sweating as did injection of the otic ganglion. No effect was obtained after blocking the sympathetic at the superior cervical ganglion. The authors conclude that the only satisfactory explanation for the phenomenon is aberrant parasympathic nerve regeneration.

## CASE REPORTS.

*Case 1.* J. Z., 651219. In April, 1956, this 41-year-old white female had undergone a subtotal parotidectomy for a mixed tumor of the right parotid. The postoperative period was uneventful. Eighteen months later she stated that her right cheek began to flush and "the gland began to leak" when she was eating. Examination revealed a well-healed incision, normal facial movements and no evidence of recurrent tumor. Upon eating an apple typical flushing and profuse sweating were observed. The Starch-iodine test (see Fig. 1) showed sweating distributed over the area of skin supplied by the auriculo-temporal and great auricular nerves. On learning that the condition was not serious the patient did not want any treatment.

*Case 2.* A.S., 708755. This 41-year-old housewife was seen at the University of Chicago Clinic on July 15, 1958, by Dr. Dwight Clark. Two and one-half years previously she had undergone subtotal parotidectomy elsewhere for a chronic parotid infection. Since the operation she complained of severe intermittent pain and recurrent swelling about the parotid area. Sometime later she noted sweating and flushing of the right cheek. A diagnosis of Frey's syndrome was made, and the patient was admitted to the hospital for study. The Starch-iodine test (see Fig. 2) revealed gustatory sweating over the distribution of the auriculotemporal nerve, and flushing of the skin was noted over the same area. A neurological consultant found no organic basis for the pain and considered it to be functional. There was no evidence of swelling about the operative site at any time while she was under our observation. Novocaine injection of the right otic ganglion by Dr. S. Mullan temporarily abolished the phenomenon. Sectioning of Jacobson's nerve in the middle ear was advised but was refused by the patient.

## DISCUSSION.

Recent studies have confirmed the thesis that the sweating and flushing were due to aberrant regeneration of parasympathic nerve fibers which were interrupted at surgery. Parasympathic secretory fibers to the parotid gland[12,13,14] originate in the inferior salivary nucleus in the medulla. They leave the brain with the glossopharyngeal nerve and enter the middle ear as Jacobson's nerve, which emerges on the roof of the petrous pyramid as the lesser superficial petrosal nerve. They enter the infratemporal fossa via the cannaliculus innominatus or the foramen ovale. The fibers synapse with ganglion cells in the otic ganglion which is just below the base of the skull, medial to the mandibular nerve. The post ganglionic fibers reach the parotid via the auriculo-temporal nerve, which also contains sensory fibers to the skin and sympathic fibers to the sweat glands and blood vessels of the skin.

After the auriculo-temporal nerve has been cut the parasympathic fibers regenerate along sympathetic pathways in the auriculo-temporal nerve and sometimes in the great auricular nerve. After a latent period of between five weeks and one year the normally sympathetic innervated sweat glands and blood vessels of the skin acquire a parasympathic nerve supply. Thus, when the patient eats he gets a reflex flushing and sweating instead of a reflex stimulation of parotid salivary flow.

Most cases are very mild and require no therapy. If symptoms are severe enough to warrant treatment, 3 per cent Scopolamine cream applied locally as recommended by Laage-Hellman[9] seems to be effective. I would suggest sectioning Jacobson's nerve in the middle ear as a safe effective treatment. The operation was described by Lempert[15] several years ago as a treatment for tinnitus aurium. Plugging the bony canal from which the nerve emerges would effectively prevent regeneration, although preganglionic parasympathic fibers do not regenerate as easily as post ganglionic fibers. Experiments are now underway in our laboratories to determine the effect of sectioning Jacobson's nerve[16] on parotid secretion.

SUMMARY.

Recent excellent work on Gustatory Sweating and Flushing is reviewed.

Two illustrative cases after subtotal parotidectomy are presented. Sectioning Jacobson's nerve on the promontory is feasible and should give permanent relief.

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Barry J. Anson, Ph.D. (Med. Sc.);
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Tissue Reaction Following Reconstruction of the Oval Window in Experimental Animals.

Richard J. Bellucci, M.D., and
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Human Cochlear Responses to Sound Stimuli.

John L. Bordley, M.D.;
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Some Physiological Factors in Inner Ear Deafness.

Merle Lawrence, Ph.D.

Distribution of Hearing Loss in Various Population Centers.

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Experiences with the Stapedectomy Technique of Shea for the Surgical Treatment of Otosclerosis.

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Secretary: Dr. Will P. Pirkey, Denver, Colo.

### COLUMBUS, OHIO, OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. John E. Arthur.
Secretary: Dr. M. L. Battles.
Meetings: First Monday of October through May, University Club, Columbus, O.

### DALLAS ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Edward A. Newell.
Vice-President: Dr. Thomas M. McCrory.
Secretary-Treasurer: Dr. James L. Baldwin, 1627 Medical Arts Bldg., Dallas, Tex.

### FEDERACION ARGENTINA, DE SOCIEDADES DE OTORRINOLARINGOLOGIA.

Secretary of the Interior: Prof. Dr. Atilio Viale del Carril.
Secretary of the Exterior: Dr. Aldo G. Remorino.
Secretary Treasury: Prof. Dr. Antonio Carrascosa.
Pro-Secretary of the Interior: Prof. Dr. Carlos P. Mercandino.
Pro-Secretary of the Exterior: Prof. Dr. Jaime A. del Sel.
Pro-Secretary of the Treasury: Dr. Jorge Zubizarreta.

### FIRST CENTRAL AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY.

President: Dr. Victor M. Noubleau, San Salvador.
Secretary-Treasurer: Dr. Hector R. Silva, Calle Arce No. 84, San Salvador, El Salvador, Central America.

### FLORIDA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. G. Dekle Taylor, Jacksonville, Fla.
President-Elect: Dr. Kenneth S. Whitmer, Miami, Fla.
First Vice-President: Dr. William H. Anderson, Jr., Ocala, Fla.
Second Vice-President: Dr. Marion W. Hester, Lakeland, Fla.
Secretary-Treasurer: Dr. Joseph W. Taylor, Jr., 1 Davis Blvd., Tampa 6, Fla.

### FOURTH LATIN-AMERICAN CONGRESS OF OTORINOLARINGOLOGIA.

President: Dr. Dario.
Secretary:
Meeting:

### FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Van D. Rathgeber.
Vice-President: Dr. William Skokan.
Secretary-Treasurer: Dr. Paul Rockwell.

### GREATER MIAMI EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Mariano C. Caballero.
Vice-President: Dr. Joseph Freeman.
Secretary-Treasurer: Dr. H. Carlton Howard.
Meeting: Quarterly in March, May, October and December on the second Thursday of the month, 6:30 P.M., at the McAllister Hotel, Miami, Fla.

### INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY.

President: Dr. Jo Ono, Tokyo, Japan.
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting:

### KANSAS CITY SOCIETY OF OTOLARYNGOLOGY AND OPHTHALMOLOGY.

President: Dr. Clarence H. Steele.
President-Elect: Dr. Dick H. Underwood.
Secretary: Dr. James T. Robison, 4620 J. C. Nichols Parkway, Kansas City, Mo.
Meeting: Third Thursday of November, January, February and April.

### LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Max E. Pohlman.
Secretary-Treasurer: Dr. Wendell C. Irvine.
Chairman of Ophthalmology Section: Dr. Carroll A. McCoy.
Secretary of Ophthalmology Section: Dr. Philip D. Shanedling.
Chairman of Otolaryngology Section: Dr. Robert W. Godwin.
Secretary of Otolaryngology Section: Dr. Francis O'N. Morris.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd., Los Angeles, Calif.
Time: 6:30 P.M. last Monday of each month from September to June, inclusive—Otolaryngology Section. 6:30, first Thursday of each month from September to June, inclusive—Ophthalmology Section.

### LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. Lucian W. Alexander, 921 Canal St., New Orleans, La.
Secretary: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.
Meeting: Edgewater Gulf Hotel, Edgewater Park, Miss., April 8-9, 1960.

## MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Members serve as chairmen in alphabetical order monthly.
Secretary-Treasurer: Dr. Roland H. Myers, 1720 Exchange Bldg., Memphis, Tenn.
Assistant Secretary-Treasurer: Dr. William F. Murrah, Jr., Exchange Bldg., Memphis, Tenn.
Meeting: Second Tuesday in each month at 8:00 P.M. at Memphis Eye, Nose and Throat Hospital.

## MEXICAN ASSOCIATION OF PLASTIC SURGEONS.

President: Dr. Cesar LaBoide, Mexico, D. F.
Vice-President: Dr. M. Gonzales Ulloa, Mexico, D. F.
Secretary: Dr. Juan De Dios Peza, Mexico, D. F.

## MEXICAN SOCIETY OF OTOLARYNGOLOGY.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela, Petrarca 332-1, Mexico 5, D. F.

## MISSISSIPPI VALLEY MEDICAL SOCIETY.

President: Dr. Arthur S. Bristow, Princeton, Mo.
Secretary-Treasurer: Dr. Harold Swanberg, Quincy, Ill.
Assistant Secretary-Treasurer: Dr. Jacob E. Reisch, Springfield, Ill.

## NETHERLANDS SOCIETY OF OTO-RHINO-LARYNGOLOGY.
(Nederlandsche Keel-Neus-Oorheelkundige Vereeniging.)

President: Dr. H. Navis, Sonsbeekweg 6, Arnhem.
Secretary: Dr. W. H. Struben, J. J. Viottastraat 1, Amsterdam.
Treasurer: Mrs. F. Velleman-Pinto, Jac. Ohrechtstr. 66, Amsterdam.

## NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. J. C. Peele, Kinston Clinic, Kinston, N. C.
Vice-President: Dr. George E. Bradord, Winston-Salem, N. C.
Secretary-Treasurer: Dr. J. D. Stratton, 1012 Kings Drive, Charlotte 7, N. C.
Meeting:

## NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.

President: Mr. G. L. Thompson, 16 Ramshill Road, Scarborough, Yorkshire.
Vice-President: Mr. J. H. Otty, Frizley Old Hall, Frizinghall Road, Bradford, Yorkshire.
Secretary and Treasurer: Mr. R. Thomas, 27 High Petergate, York, Yorkshire.

## OREGON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. David D. DeWeese, 1216 S. W. Yamhill St., Portland 5, Ore.
Secretary-Treasurer: Dr. Paul B. Myers, 223 Medical Dental Bldg., Portland 5, Ore.
Meeting: Fourth Tuesday of each month from September through May, Henry Thiele Restaurant, 23rd and W. Burnside, Portland, Ore.

### OTOSCLEROSIS STUDY GROUP.

President: Dr. E. H. Campbell, 133 So. 36th St., Philadelphia 4, Pa.
Secretary-Treasurer: Dr. Raymond Jordan, 121 University Place, Pittsburgh, Pa.
Meeting: Palmer House, Chicago, Ill., October, 1960.

### PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY.

President: Dr. John F. Tolan, 1118 - 9th Ave., Seattle 5, Wash.
Secretary-Treasurer: Dr. Homer E. Smith, 686 Twelfth Ave., Salt Lake City, Utah.
Meeting:

### PAN AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Paul Holinger, 700 No. Michigan Blvd., Chicago, Ill.
Executive Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting: Seventh Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology.
Time and Place: Miami, Fla., March, 1960.

### PHILADELPHIA LARYNGOLOGICAL SOCIETY.

President Dr. John J. O'Keefe.
Vice-President: Dr. Joseph P. Atkins.
Secretary: Dr. William A. Lell.
Executive Committee: Dr. Harry P. Schenck, Dr. Benjamin H. Shuster, Dr. William A. Lell, Dr. William J. Hitschler, and Dr. Chevalier L. Jackson.

### PHILIPPINE SOCIETY OF OTOLARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Macario G. Tan, 426 Evangelista, Manila, P. I.
Vice-President: Dr. Ariston G. Bautista, 460 Isaac Peral, Manila, P. I.
Secretary-Treasurer: Dr. Angel Enriquez, American Hospital, Aduana St., Manila, P. I.

### PITTSBURGH OTOLOGICAL SOCIETY.

President: Dr. Emory A. Rittenhouse, 203 Masonic Bldg., McKeesport, Pa.
Vice-President: Dr. Carson S. Demling, 513 Jenkins Bldg., Pittsburgh 22, Pa.
Secretary-Treasurer: Dr. Clyde B. Lamp, 8101 Jenkins Arcade, Pittsburgh 22, Pa.

### PORTUGUESE OTORHINOLARYNGOLOGICAL SOCIETY.

President: Dr. Albert Luis de Mendonca.
Secretary: Dr. Antonio da Costa Quinta, Avenida, de Liberdale 65, 1° Lisbon.

### PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Clifton E. Benson, Bremerton, Wash.
President-Elect: Dr. Carl D. F. Jensen, Seattle, Wash.
Secretary: Dr. Willard F. Goff, 1215 Fourth Ave., Seattle, Wash.

### SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

Meeting: University of Vienna, August 29 to September 1, 1960.

## RESEARCH STUDY CLUB OF LOS ANGELES, INC.

Chairman: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Treasurer: Dr. Norman Jesberg, 500 So. Lucas Ave., Los Angeles 17, Calif.
Otolaryngology: Dr. Russell M. Decker, 65 N. Madison Ave., Pasadena 1, Calif.
Ophthalmology: Dr. Warren A. Wilson, 1930 Wilshire Blvd., Los Angeles 57, Calif.
Mid-Winter Clinical Convention annually, the last two weeks in January at Los Angeles, Calif.

## SECTION ON OTOLARYNGOLOGY OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA.

Chairman: Dr. Morris E. Krucoff.
Vice-Chairman: Dr. Max J. Fischer.
Secretary: Dr. Adrian J. Delaney.
Treasurer: Dr. Robert D. Ralph.
Meetings are held the second Tuesday of September, November, January, March and May, at 6:30 P.M.
Place: Army and Navy Club, Washington, D. C.

## SCOTTISH OTOLARYNGOLOGICAL SOCIETY.

President: Dr. F. T. Land, 13 Newton Place, Glasgow, C. 3.
Secretary-Treasurer: Dr. J. F. Birrell, 14 Moray Place, Edinburgh.
Assistant Secretary: Dr. H. D. Brown Kelly, 11 Sandyford Place, Glasgow, C. 3.

## SOCIEDAD COLUMBIANA DE OFTALMOLOGIA Y OTORRINOLARINGOLOGIA (BOGOTA, COLUMBIA).

Presidente: Dr. Alfonso Tribin P.
Secretario: Dr. Felix E. Lozano.
Tesorero: Dr. Mario Arenas A.

## SOCIEDAD CUBANA DE OTO-LARINGOLOGIA.

President: Dr. Reinaldo de Villiers.
Vice-President: Dr. Jorge de Cárdenas.
Secretary: Dr. Pablo Hernandez.

## SOCIEDAD DE ESTUDIOS CLINICOS DE LA HABANA.

Presidente: Dr. Frank Canosa Lorenzo.
Vice-Presidente: Dr. Julio Sanguily.
Secretario: Dr. Juan Portuondo de Castro.
Tesorero: Dr. Luis Ortega Verdes.

## SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOSCOPIA DE CORDOBA.

Presidente: Dr. Aldo Remorino.
Vice-Presidente: Dr. Luis E. Olsen.
Secretario: Dr. Eugenio Romero Diaz.
Tesorero: Dr. Juan Manuel Pradales.
Vocales: Dr. Osvaldo Suárez, Dr. Nondier Asis R., Dr. Jorge Bergallo Yofre.

## SOCIEDAD DE OTO-RINO-LARINGOLOGIA, COLEGIO MEDIO DE EL SALVADOR, SAN SALVADOR, C. A.

President: Dr. Salvador Mixco Pinto.
Secretary: Dr. Daniel Alfredo Alfaro.
Treasurer: Dr Antonio Pineda M.

### SOCIEDAD ESPANOLA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. D. Adolfo Hinojar Pons.
Vice-Presidente: Dr. D. Jose Perez Mateos.
Secretario General: Dr. D. Francisco Marañés.
Tesorero: Dr. D. Ernesto Alonso Ferrer.

### SOCIEDAD MEXICANA DE OTORRINOLARINGOLOGIA

Monterrey 47-201
Mexico 7, D. F.

President: Dr. Rafael Giorgana.
Secretary: Dr. Carlos Valenzuela.
Treasurer: Dr. Benito Madariaga.
First Vocal: Dr. Rafael González.
Second Vocal: Dr. Juan Oberhauser.

### SOCIEDAD NACIONAL DE CIRUGIA OF CUBA.

Presidente: Dr. Reinaldo de Villers.
Vice-Presidente: Dr. César Cabrera Calderin.
Secretario: Dr. José Xirau.
Tesorero: Dr. Alfredo M. Petit.
Vocal: Dr. José Gross.
Vocal: Dr. Pedro Hernández Gonzalo.

### SOCIEDAD OTO-RINO-LARINGOLOGIA DE LOS HOSPITALES DE MADRID.

Presidente: Dr. Don Fernando Beltrán Castillo.
Secretario General: Dr. Don Alfonso Vassallo de Mumbert.
Tesorero: Dr. Don Rafael Garcia Tapia.

### SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOLOGIA DEL NORESTE.

Presidente: Dr. Livio M. Lataza C.
Secretario: Dr. Ramón Prieto.
Tesorero: Dr. José Gomez Galizia.
Vocales: Dres. Enrique del Buono y O. Benjamín Serrano.

### SOCIEDAD VENEZOLANA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Gabriel Briceño Romero.
Vice-Presidente: Dr. Silvestre Rincón Fuenmayor.
Secretario General: Dr. Oscar Bustamante Miranda.
Tesorero: Dr. Arturo Marrero Gómez.
Vocales: Dr. Miguel Octavio Russa, Dr. Benjamin Briceño, Dr. Oscar Gonzalez Castillo.

### SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DO RIO GRANDE DO SUL.

President: Dr. Ivo Adolpho Kuhl.
Secretary: Dr. Decio Lisboa Castro.
Treasurer: Dr. Jorge Valentin.

### SOCIEDAD PANAMENA DE OTORRINOLARINGOLOGIA.

Presidente: Dr. Manuel Preciado.
First Vice-Presidente: Dr. Alonso Roy.
Second Vice-Presidente: Dr. Carlos Arango Carbone.
Secretario: Dr. Maria Esther Villalaz.
Tesorero: Dr. Ramòn Crespo.

## SOCIEDADE PORTUGUESA DE OTORRINOLARINGOLOGIA E DE BRONCO-ESOFAGOLOGIA.

Presidente: Dr. Alberto Luis De Mendonca.
Vice-Presidente: Dr. Jaime de Magalhaes.
1.° Secretario: Dr. Antonio da Costa Quinta.
2.° Secretario: Dr. Albano Coelho.
Tesoureiro: Dr. Jose Antonio de Campos Henriques.
Vogais: Dr. Teofilo Esquivel.
Dr. Antonio Cancela de Amorim.
Sede: Avenida da Liberdade, 65, 1°, Lisboa.

## SOCIETY OF MILITARY OTOLARYNGOLOGISTS.

President: Lt. Col. Stanley H. Bear, USAF (MC), USAF Hospital, Maxwell (Air University), Maxwell Air Force Base, Ala.
Secretary-Treasurer: Capt. Maurice Schiff, MC, USN, U. S. Naval Hospital, Oakland, Calif.
Meeting:

## SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. F. R. Price, 118 Rutledge Ave., Charleston, S. C.
President-Elect: Dr. L. D. Lide, 161 W. Cheves St., Florence, S. C.
Vice-President: Dr. R. E. Livingstone, 1505 Main St., Newberry, S. C.
Secretary-Treasurer: Dr. Roderick Macdonald, 330 E. Main St., Rock Hill, S. C.

## SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Dr. George M. Haik, Professor and Head of the Department of Ophthalmology at Louisiana State University School of Medicine, 812 Maison Blanche Building, New Orleans 16, La.
Chairman-Elect: Dr. Mercer G. Lynch, Assistant Professor of Otolaryngology, Tulane University School of Medicine, 3503 Prytania St., New Orleans 15, La.
Vice-Chairman: Dr. Bernard J. McMahon, Director of the Department and Clinical Professor of Otolaryngology, St. Louis University School of Medicine, 8230 Forsythe Blvd., Clayton 24, Mo.
Secretary: Dr. Albert C. Esposito, First Huntington National Bank Building, Huntington, W. Va. Formerly instructor of Ophthalmology, Ohio State University College of Medicine, Columbus, O.
Meeting: St. Louis, Mo., October 31, 1960, to November 3, 1960.

## VIRGINIA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Benjamin Sheppard, 301 Medical Arts Building, Richmond, Va.
President-Elect: Dr. Emanuel U. Wallerstein, Professional Building, Richmond, Va.
Vice-President: Dr. Calvin T. Burton, Medical Arts Building, Roanoke, Va.
Secretary-Treasurer: Dr. Maynard P. Smith, 600 Professional Building, Richmond, Va.

## WEST VIRGINIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Nime K. Joseph, Wheeling, W. Va.
President-Elect: Dr. John A. B. Holt, Charleston, W. Va.
Vice-President: Dr. William K. Marple, Huntington, W. Va.
Secretary-Treasurer: Dr. Albert C. Esposito, Huntington, W. Va.
Director for Two Years: Dr. James T. Spencer, Charleston, W. Va.